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In this issue–

SYMPOSIUM ON NUCLEAR MEDICINE

CHAIRMAN'S ADDRESS—J. R. Maxfield, Jr. 385

ADDRESS OF WELCOME—George J. Hearn 385

SOME FUNDAMENTALS OF RADIOLOGIC PHYSICS—Thomas G. Mitchell 386

IMPORTANT APPLICATIONS OF NUCLEAR MEDICINE IN PATHOLOGY—Oscar B. Hunter, Jr. 400

THE INTERNIST'S VIEWPOINT ON THE USE OF RADIOACTIVE IODINE IN THYROID DISORDERS AND CARDIAC ABNORMALITIES

I. DIAGNOSTIC PROCEDURES FOR THE ESTIMATION OF THYROID FUNCTION—George E. Thoma, Jr. 405

II. THERAPEUTIC CONSIDERATIONS IN THE USE OF RADIOIODINE IN THYROTOXICOSIS—Samuel B. Nadler 411

RADIOLOGICAL USES OF RADIOACTIVE MATERIALS—Wynton H. Carroll 414

THE RADIOISOTOPIC LOCALIZATION OF INTRACRANIAL NEOPLASIA UTILIZING THE FOCUSING COLLIMATOR SCINTILLATION COUNTER WITH PHOTOSCAN ATTACHMENT—David R. Taxdal and John G. McAfee 418

A SURGEON VIEWS RADIOACTIVE IODINE AND THE THYROID PROBLEM—Lindon Seed 424

WHAT EVERY DOCTOR SHOULD KNOW ABOUT "FALLOUT"—David I. Livermore 429

THE MANAGEMENT OF VICTIMS OF RADIATION ACCIDENT—E. R. King 432

HEMORRHAGIC DIATHESIS ASSOCIATED WITH LONG-TERM ANTICOAGULANT THERAPY—Paul W. Boyles 441

STUDIES RELATING TO CREEPING ERUPTION—J. M. Hitch and V. Iralu 447

PRIMARY HYPERCHOLESTEREMIA AND IDIOPATHIC HYPERLIPEMIA: CLINICAL, BIOCHEMICAL AND THERAPEUTIC CONSIDERATIONS—Walter F. Lever 454

Continued on cover 2

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CONTENTS

Continued from cover 1

USE OF BIPERIDEN HYDROCHLORIDE IN PARKINSON'S DISEASE —Philip F. Lerner 465

RADIOACTIVE FAT TOLERANCE STUDIES IN CORONARY ARTERY DISEASE—Donald Berkowitz, John J. Spitzer, David M. Sklaroff, and William Likoff 468

THE VULVAR CLINIC: A TEACHING AND RESEARCH PROJECT—Herbert W. Birch and Jason H. Collins 473

TWENTY-TWO YEARS' EXPERIENCE IN THE PERFORMANCE OF 200,000 PROPHETIC PATCH TESTS—Louis Schwartz 478

PLACENTA AND CORD—VULNERABLE FETAL SUPPORT—Clyde L. Randall 484

REHABILITATION IN RHEUMATOID ARTHRITIS—William D. Paul 492

PRIMARY NEOPLASMS OF THE URETER—Seymour Fiske Ochsner and William Brannan 497

A NEW TREATMENT OF RADIO-ULNAR SYNOSTOSIS—Louis P. Brady and Eugene L. Jewett 507

TOTAL ESOPHAGOPLASTY BY UTILIZING THE COLON—Robert P. McBurney 513

TOTAL COLONOSCOPY: A SYSTEMATIC SURGICAL APPROACH—James A. Ferguson 517

KNOW YOUR SOUTHERN MEDICAL ASSOCIATION 520

SOUTHERN MEDICAL NEWS 521

EDITORIALS 522

Glomerular and Retinal Lesions in Diabetes Mellitus

Symposium on Nuclear Medicine

INSTRUCTIONS TO CONTRIBUTORS 523

TWENTY-FIVE YEARS AGO 524

BOOKS RECEIVED 524

OFFICERS OF THE SOUTHERN MEDICAL ASSOCIATION 1959-1960 527

BOOK REVIEWS 530

SOUTHERN MEDICAL ASSOCIATION GROUP DISABILITY PLAN MEETS A GREAT NEED 532

INDEX TO ADVERTISERS ..... Adv. Page 96

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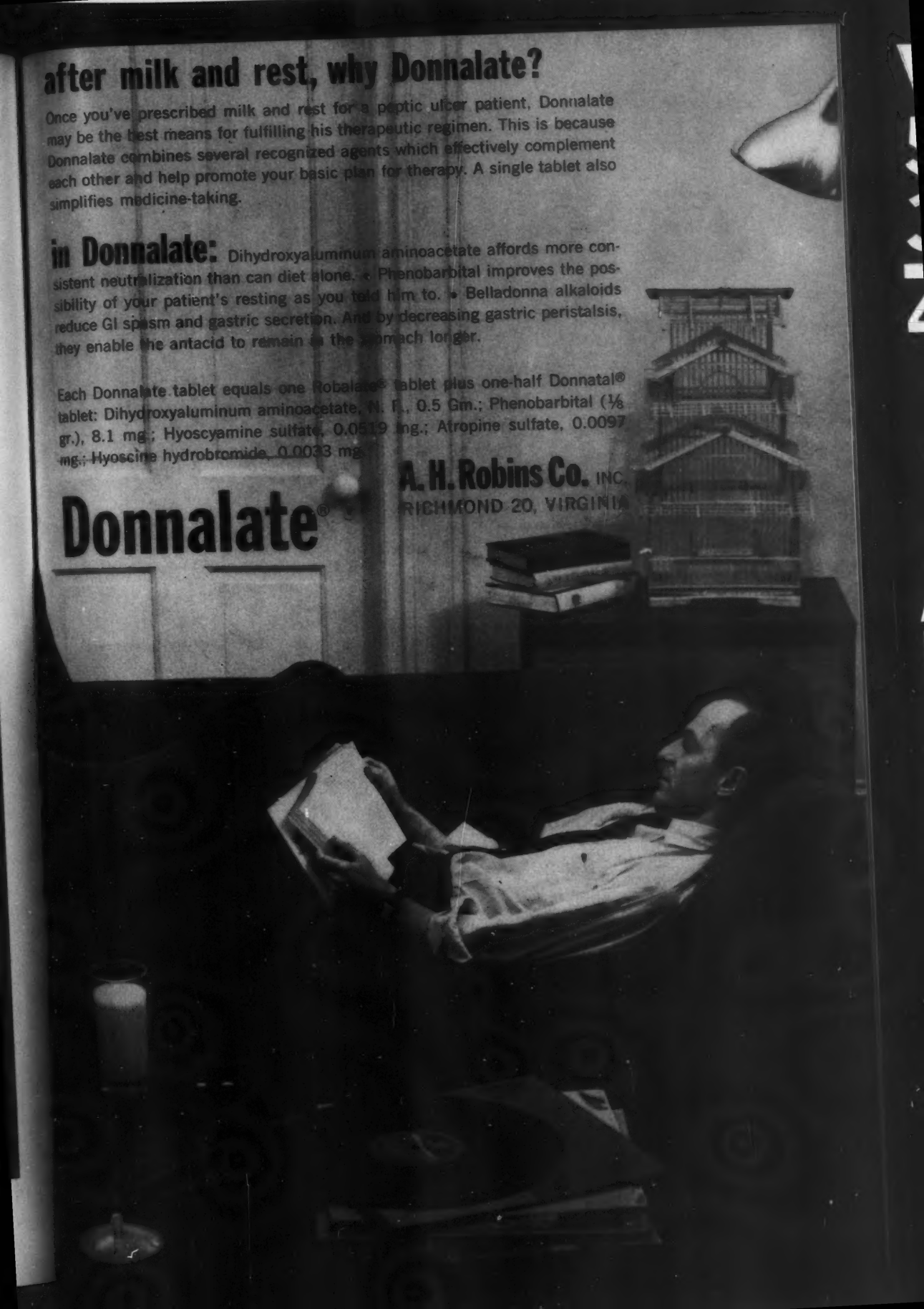

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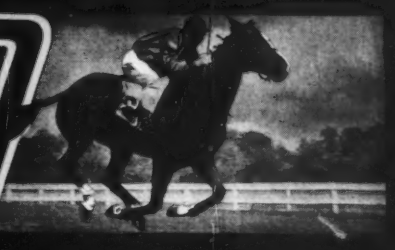

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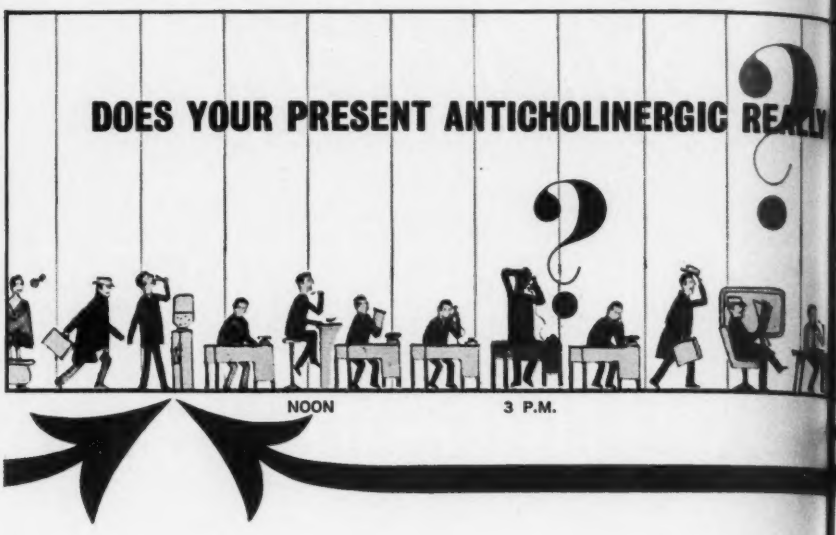

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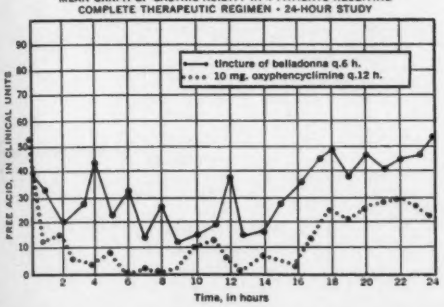

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References: 1. McHardy, G., et al.: J. Louisiana M. Soc. 111:290 (Aug.) 1959. 2. Steigmann, F.: Study conducted at Cook County Hospital, Chicago, Illinois, in press. 3. Kemp, J. A.: Antibiotic Med. & Clin. Therapy 6:534 (Sept.) 1959. 4. Leming, B. H., Jr.: Clin. Med. 6:423 (Mar.) 1959. 5. Data in Roerig Medical Department files.

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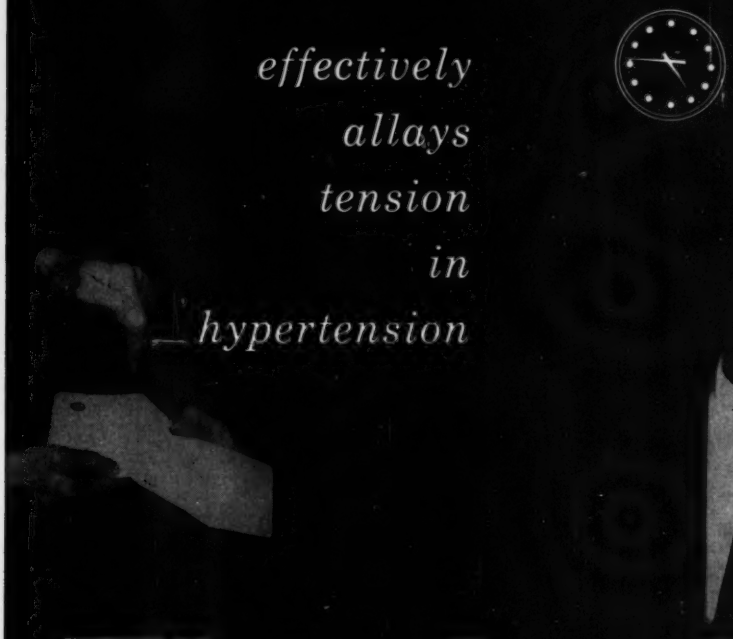

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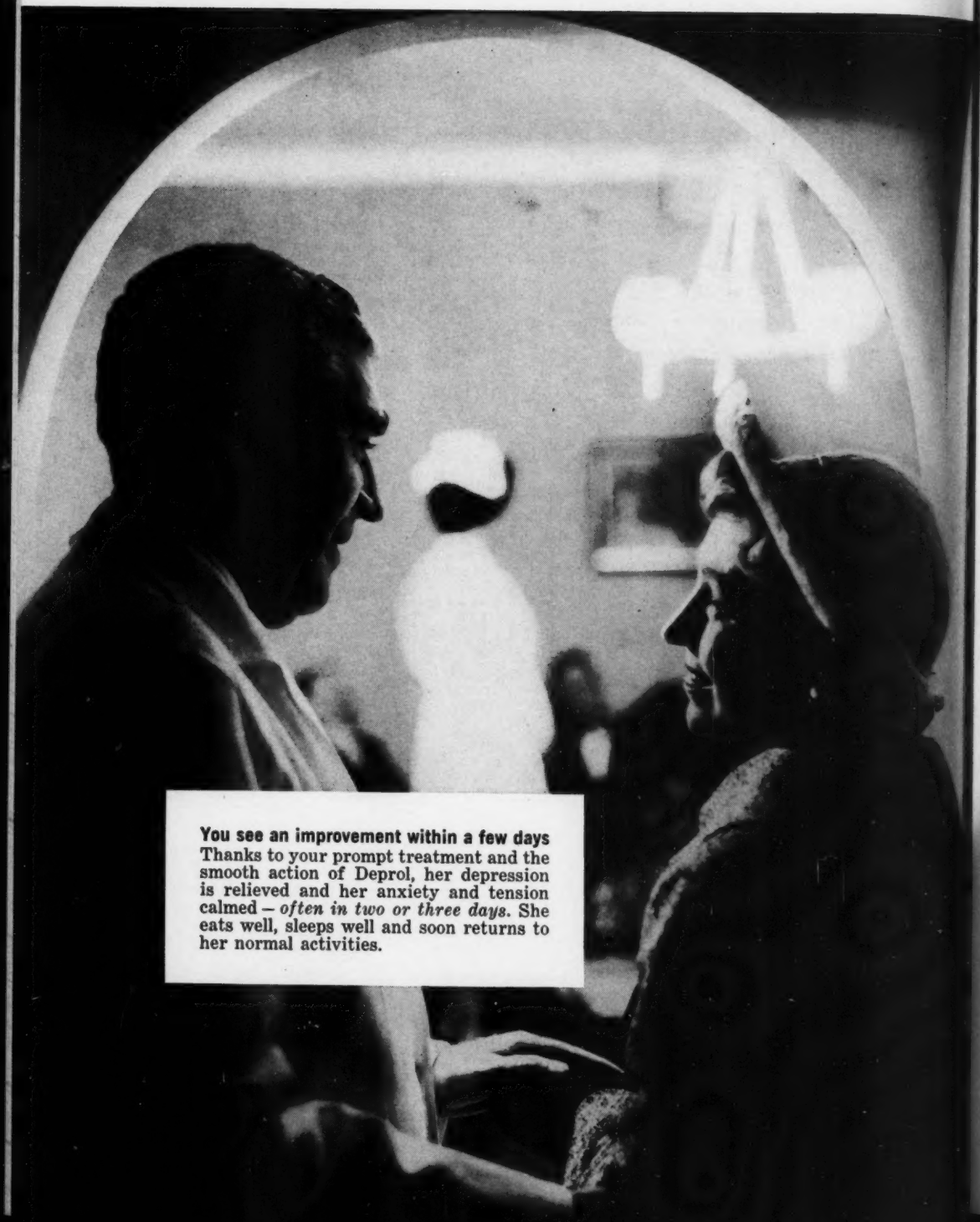

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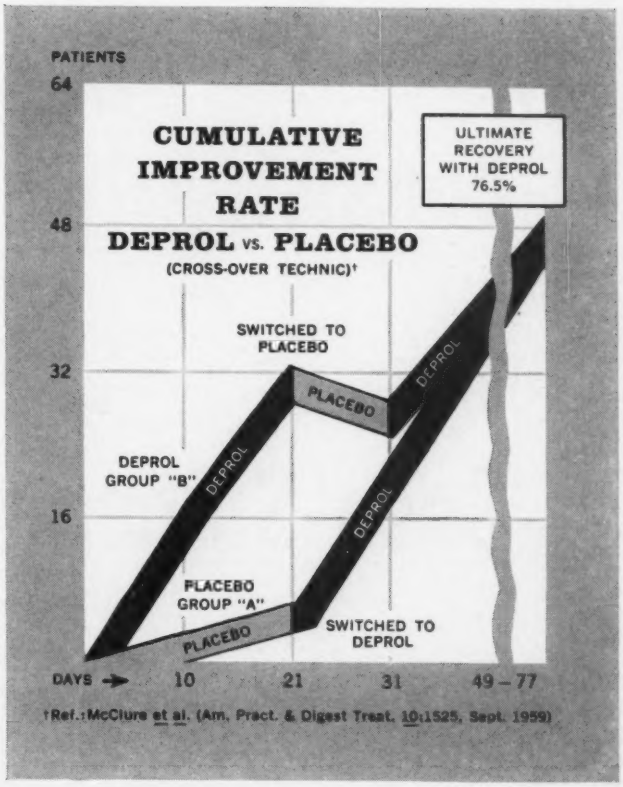

†Ref.: McClure et al. (Am. Pract. & Digest Treat. 10:1525, Sept. 1959)

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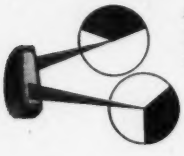

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1. Fabricant, N. D.: E.E.N.T. Monthly *37*:460 (July) 1958.
2. Lhotka, F. M.: Illinois M. J.: *113*:259 (Dec.) 1957.
3. Farmer, D. F.: Clin. Med. *5*:1183 (Sept.) 1958.

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Analexin is a new synthetic chemical, phenyramidol hydrochloride (2[β-hydroxy-phenethylamino]-pyridine hydrochloride) that inherently possesses two different pharmacologic actions within one molecular structure:[1,2] (1) *general analgesia* by raising the pain threshold and thus decreasing the perception of pain, and (2) *muscle relaxation* by selectively depressing subcortical, brain stem and polysynaptic transmission (interneuronal blockade), abolishing abnormal muscle tone without impairment of normal neuromuscular function. Thus in painful states, Analexin relieves both the pain and the muscle tension that augments the pain, and manages the total pain experience more effectively.

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Analexin is not related to any currently available analgesic or muscle relaxant compound. The analgesic effectiveness of one tablet is clinically equivalent to that of 1 grain of codeine; yet, Analexin is neither narcotic nor narcotic-related. It is not habituating and tolerance to the drug has not been noted. Its muscle relaxant effect is comparable to the most potent oral muscle relaxants available.[3,4] The total effect is "analgomylaxation"—a new advance for the relief of pain. The incidence of side effects is low and those reactions that have been reported occasionally (gastrointestinal irritation, pruritus) are of a mild and transient nature and do not limit therapy.[5]

Analexin . . . *for relief of pain and muscle tension.* Each tablet contains 200 mg. of phenyramidol HCl. Dosage—1 tablet every 2-4 hours or as needed.

Analexin-AF . . . *for relief of pain and muscle tension complicated by fever and/or inflammation.* Each tablet contains 100 mg. of phenyramidol HCl and 300 mg. of aluminum aspirin. Dosage—2 tablets every 4 hours or as required.

in one tablet — two actions — Analgesic *raises pain threshold* — Myolaxant *relaxes muscle tension* — **Analexin** *the first analgomylaxant*

RATIONAL THERAPY
IN A WIDE RANGE OF
COMMON SKIN DISORDERS

NEW FURACIN®-HC CREAM

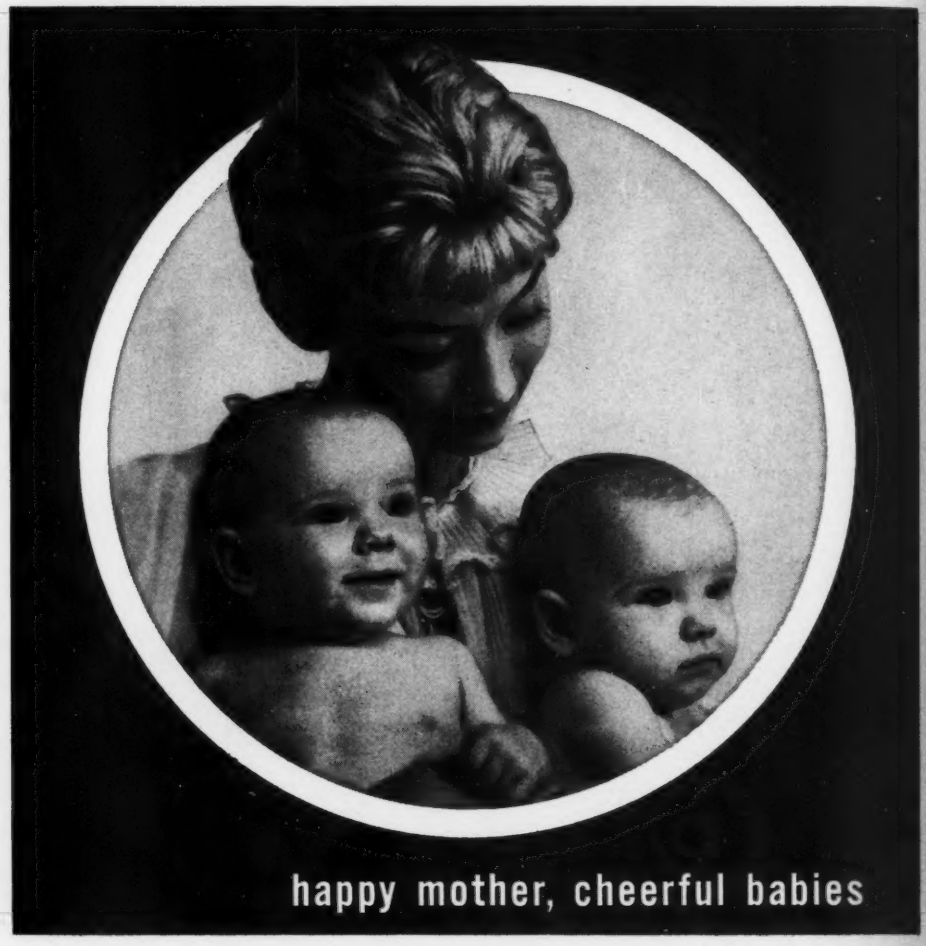
(NITROFURAZONE 0.2% AND HYDROCORTISONE 1%, EATON)

INFECTED AND POTENTIALLY INFECTED DERMATOSES / PYODERMAS / ULCERS
BURNS / AFTER PLASTIC, ANORECTAL AND MINOR SURGERY

FURACIN-HC Cream combines the anti-inflammatory and antipruritic effect of hydrocortisone with the dependable antibacterial action of FURACIN®, brand of nitrofurazone—the most widely prescribed single topical antibacterial. The broad bactericidal range of FURACIN includes stubborn staphylococcal strains, and there has been no development of significant bacterial resistance after more than a dozen years of widespread clinical use. FURACIN is gentle to tissues, does not retard healing; its low sensitization rate is further minimized by the presence of hydrocortisone.

FURACIN-HC Cream is available in tubes of 5 Gm. and 20 Gm. Fine vanishing cream base, water-soluble.

NITROFURANS—a unique class of antimicrobials / EATON LABORATORIES, NORWICH, NEW YORK
Products of Eaton Research



because their physician has kept the twins well nourished, healthy, and

free from diaper rash

with

DESITIN®

OINTMENT

Protects against irritation of urine and excrement; markedly inhibits ammonia-producing bacteria; soothes, lubricates, stimulates healing.

For samples of Desitin Ointment, pioneer external cod liver oil therapy, write...

DESITIN CHEMICAL COMPANY
812 Branch Avenue, Providence 4, R. I.

SYNDROX®

McNEIL

in edema of pregnancy

"gratifying relief..."

in all patients

treated with

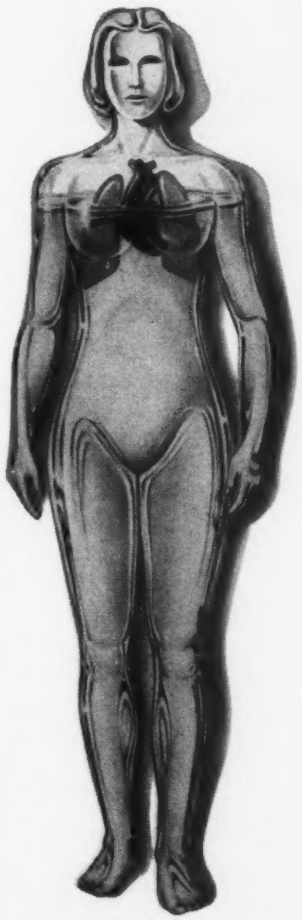
HYDRODIURIL®

HYDROCHLOROTHIAZIDE

increased potency–without corresponding increase in side effects

Ford, Ralph V.: Southern Med. Jl. 52: 40, (Jan.) 1959

"Hydrochlorothiazide was given to patients with edema (mild to moderate) of varied etiology..." "There were...5 women in the third trimester of pregnancy." In these patients the cumulative weight loss was 2 pounds after seven days of therapy and 4 pounds after twenty-one days. Gratifying relief of edema was observed in all patients.



DOSAGE: One or two 50 mg. tablets HYDRODIURIL once or twice a day, depending upon the condition and individual patient response.

SUPPLIED: 25 mg. and 50 mg. scored tablets HYDRODIURIL (Hydrochlorothiazide) in bottles of 100 and 1,000.

HYDRODIURIL is a trademark of Merck & Co., INC.

Additional information on HYDRODIURIL is available to the physician on request. ©1960 Merck & Co., INC.

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GOOD SERVICE

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When you buy an electrocardiograph*, the manufacturer has two obligations to you:

...to provide the best possible instrument for your needs

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As a Sanborn owner, you receive this continuing service in many forms, through nearby Branch Offices, Service Agencies and Resident Representatives in 46 cities: "emergency" calls when required, and prompt response to routine requests for supplies and accessories . . . ECG Study Courses (by correspondence); the bi-monthly Sanborn Technical Bulletin; comprehensive instrument Instruction Manuals . . . and a Question and Answer Service for any problems in the use of Sanborn instruments.

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*From Sanborn, you now have a choice of the 2-speed Model 100 Viso-Cardiette . . . its mobile counterpart the Model 100M "Mobile Viso" . . . or the compact, fully portable 18-pound Model 300 Visette.

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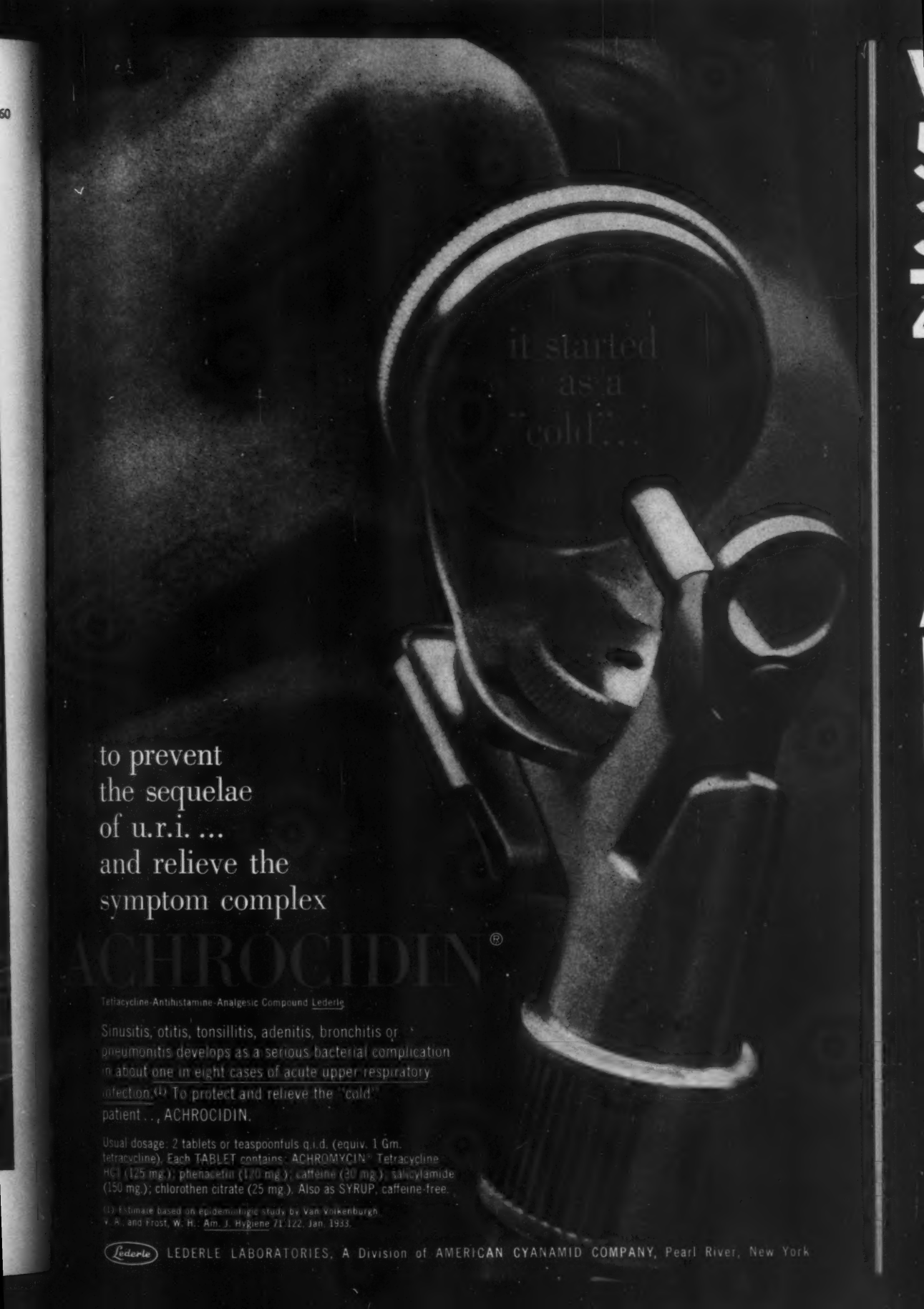


to prevent the sequelae of u.r.i. ... and relieve the symptom complex

ACHROCIDIN®

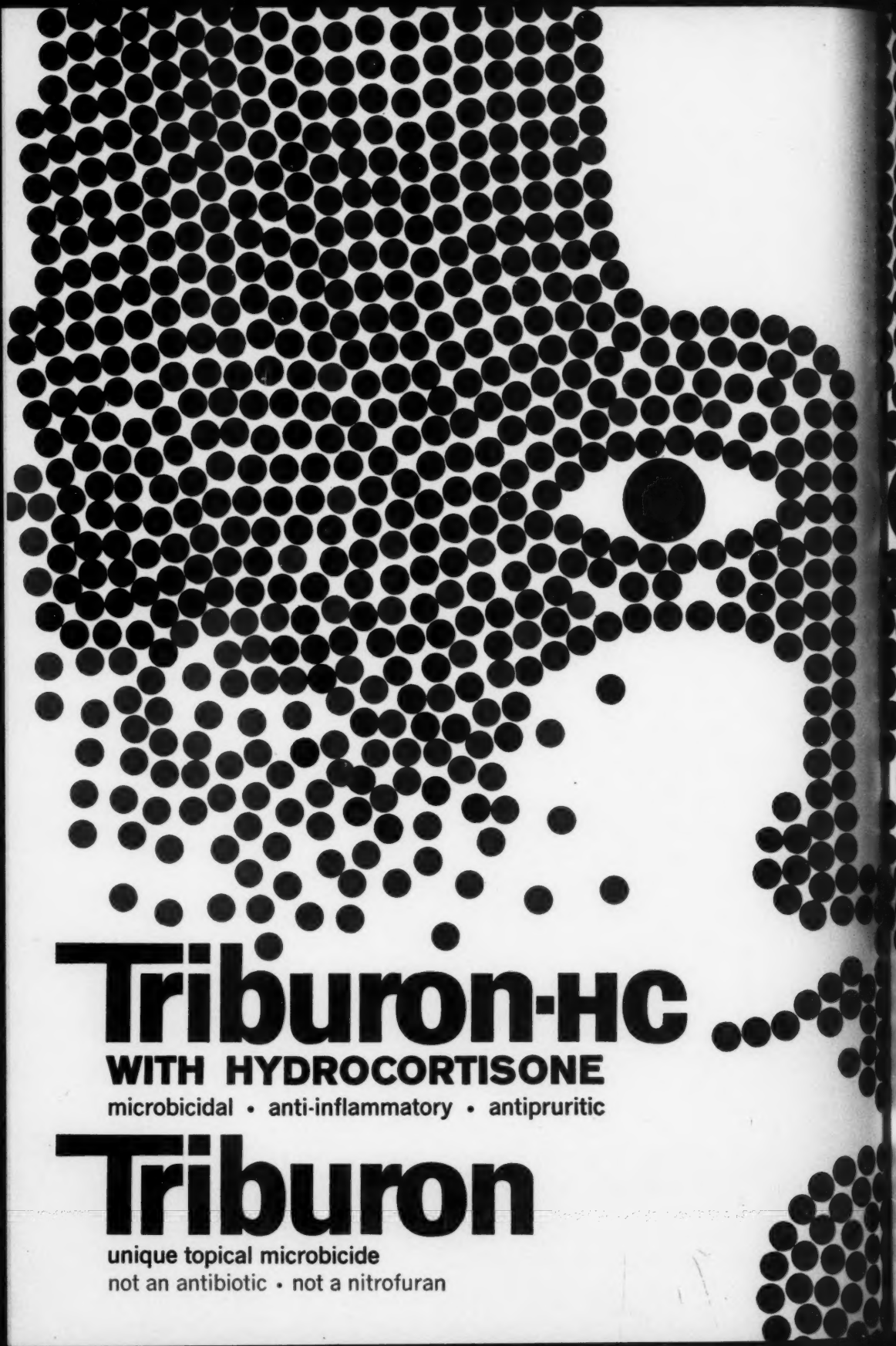
Tetracycline-Antihistamine-Analgesic Compound Lederle

Sinusitis, otitis, tonsillitis, adenitis, bronchitis or pneumonitis develops as a serious bacterial complication in about one in eight cases of acute upper respiratory infection.(1) To protect and relieve the "cold" patient . . , ACHROCIDIN.

Usual dosage: 2 tablets or teaspoonfuls q.i.d. (equiv. 1 Gm. tetracycline). Each TABLET contains: ACHROMYCIN® Tetracycline HCl (125 mg.); phenacetin (120 mg.); caffeine (30 mg.); salicylamide (150 mg.); chlorothen citrate (25 mg.). Also as SYRUP, caffeine-free.

(1) Estimate based on epidemiologic study by Van Volkenburgh, V. A., and Frost, W. H.: Am. J. Hygiene 71:122, Jan. 1933.

Lederle LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York


Triburon-HC
WITH HYDROCORTISONE
microbicidal • anti-inflammatory • antipruritic
Triburon
unique topical microbicide
not an antibiotic • not a nitrofuran

CONSISTENT RESPONSE IN SKIN INFECTIONS

REGARDLESS OF VIRULENCE, RESISTANCE, CHRONICITY

A DISTINCTIVE ANTIMICROBIAL, TRIBURON PREVAILS OVER PRIMARY AND SECONDARY INVADERS PROMPTLY, SAFELY, WITH NO SIGNIFICANT LOSS OF ORGANISM SENSITIVITY.[1] TWO FORMS: TRIBURON FOR SKIN AND WOUND INFECTIONS, TRIBURON-HC (WITH HYDROCORTISONE) TO COUNTER ITCHING AND INFLAMMATION AS WELL AS INFECTION. BOTH HAVE ACHIEVED IMPRESSIVE CLINICAL RECORDS:

- **EFFECTIVE IN OVER 90% OF PATIENTS[2-5]**
- **DRAMATIC RESPONSES IN CHRONIC CONDITIONS[4, 6]**
- **MICROBICIDAL EVEN AGAINST RESISTANT STRAINS OF STAPH. AND STREP.[1, 4]**
- **VIRTUALLY NONSENSITIZING AND NONIRRITATING[2-5]**
- **STAINLESS, ODORLESS, "HIGHLY ACCEPTABLE"[5].**

EFFECTIVE THERAPY FOR: IMPETIGO, FOLLICULITIS, FURUNCULOSIS, ECTHYMA, ECZEMA, ACNE, ATOPIC DERMATITIS, NEURODERMATITIS, CONTACT DERMATITIS, STASIS ULCERS, HYDRADENITIS, SEBORRHEIC DERMATITIS, INFECTIOUS ECZEMATOUS DERMATITIS, WOUNDS AND LACERATIONS.

TRIBURON—FOR ALL SKIN AND WOUND INFECTIONS REQUIRING CONSISTENT ANTIBACTERIAL ACTION, AND FOR PREVENTION AND TREATMENT OF POST-BURN INFECTIONS. (TRIBURON-IMPREGNATED DRESSINGS CAN BE AUTOCLAVED.)

AVAILABLE: OINTMENT, CONTAINING 0.1 PER CENT TRIBURON CHLORIDE, IN 1-OZ TUBES AND 1-LB JARS.

TRIBURON-HC—FOR INFLAMMATORY AND ECZEMATOID DERMATOSES WHERE ANTI-INFLAMMATORY AND ANTIPRURITIC BENEFITS AS WELL AS ANTIBACTERIAL EFFECTS ARE REQUIRED.

AVAILABLE: OINTMENT, CONTAINING 0.1 PER CENT TRIBURON CHLORIDE PLUS 0.5 PER CENT HYDROCORTISONE, IN 5-GM AND 20-GM TUBES.

REFERENCES: 1. R. J. SCHNITZER, E. GRUNBERG, W. F. DELORENZO AND R. E. BAGDON, ANTIBIOTICS & CHEMOTHER., 9:267, 1959. 2. R. C. V. ROBINSON, ANN. NEW YORK ACAD. SC., 82:(ART. 1), 144, 1959. 3. E. EDELSON, E. GRUNBERG, A. D. CALABRESE AND T. V. MORTON, IBID., P. 124. 4. P. L. WILLIAMS, IBID., P. 135. 5. F. T. BECKER AND J. L. TUURA, IBID., P. 131. 6. S. M. BLUEFARB, IBID., P. 119.

TRIBURON® CHLORIDE—N,N'-BIS[1-METHYL-3-(2,2,6-TRIMETHYLCYCLOHEXYL) PROPYL]-N,N'-DIMETHYL-1,6-HEXANEDIAMINE BIS (METHOCHLORIDE)

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spreads
THINLY · EVENLY · ECONOMICALLY
in acute dermatologic conditions

SUPERTAH H-C
(1.3% COAL TAR FRACTION WITH HYDROCORTISONE [illegible])

antiinflammatory — antipruritic

- water miscible base — purified white tar fraction stainless, washable
- maximum efficiency — spreads thinly for evenly distributed therapeutic action and great economy
- enhanced benefits — more effective than either agent alone
- excellent response — deep penetration to source of inflammation

supplied: ½-oz. tube

also available:
SUPERTAH Ointment (1½-oz. tube)
provides the therapeutic effectiveness of time-proved tar medication
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for keratolytic action

All Supertah preparations are made with refined natural coal tar fraction

TAILBY-NASON COMPANY, INC. DOVER, DELAWARE

Against the "Vaginitis Spectrum"

TRICHOMONAS
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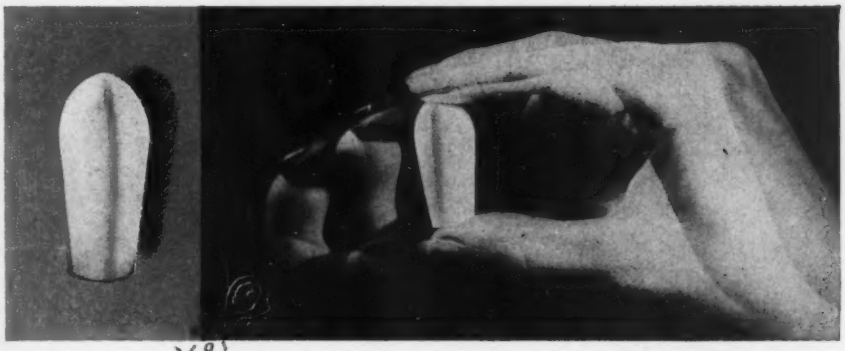
BACTERIA

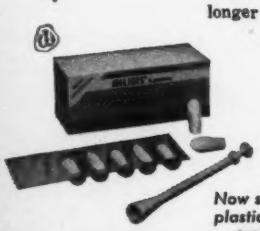
A welcome clinical advance...
effective medication
in an appealing form



Soft and pliant as a tampon, the Milibis vaginal suppository offers proved therapeutic action* in a vehicle giving unusual clinical advantages to both patients and physician.

COVERS CERVIX AND VAGINAL WALL—The pliant Milibis suppository disintegrates readily and molds itself to the cervix as well as the columns and rugae of the vaginal vault.

SHORT DOSAGE SCHEDULE—The short course of treatment with Milibis—only 10 suppositories in most cases—together with the clean, odorless, non-staining qualities eliminates psychic barriers which often interrupt longer treatments before complete cure.



SUPPLIED: BOXES OF 10 with applicator.

Now supplied with plastic applicator
- SANITARY
- INSURES CORRECT SUPPOSITORY PLACEMENT

MILIBIS® Vaginal Suppositories

Winthrop LABORATORIES
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*97 per cent effective in a study of 564 cases; 94 per cent effective in a series of 510 cases.

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Lufa®

CAPSULES

BRINGS DOWN
HOLDS DOWN **high cholesterol levels—today's**

Each LUFA capsule provides:

Unsaturated Fatty Acids**	378 mg.
Pyridoxine HCl (B_6)	2 mg.
Choline Bitartrate	233 mg.
dl, Methionine	110 mg.
Inositol	40 mg.
Desiccated Liver	87 mg.
Vitamin B_{12}	1 mcg.
Vitamin E (dl,alpha-tocopheryl acetate)	3.5 I.U.

**from specially refined safflower seed oil.
Provides approximately 294 mg. of linoleic acid.

every patient with

hypercholesterolemia

obesity

diabetes

angina pectoris

post-coronary infarction

deserves the benefit potentials of **SAFE • SIMPLE • ECONOMICAL** Lufa

1. LUFA's unsaturated fatty acids offset the atherogenic effects of dietary saturated (animal) fatty acids.*

2. LUFA helps improve metabolism of cholesterol, lipoproteins and other lipids by promoting normal liver function.

major concept in control of Atherosclerosis

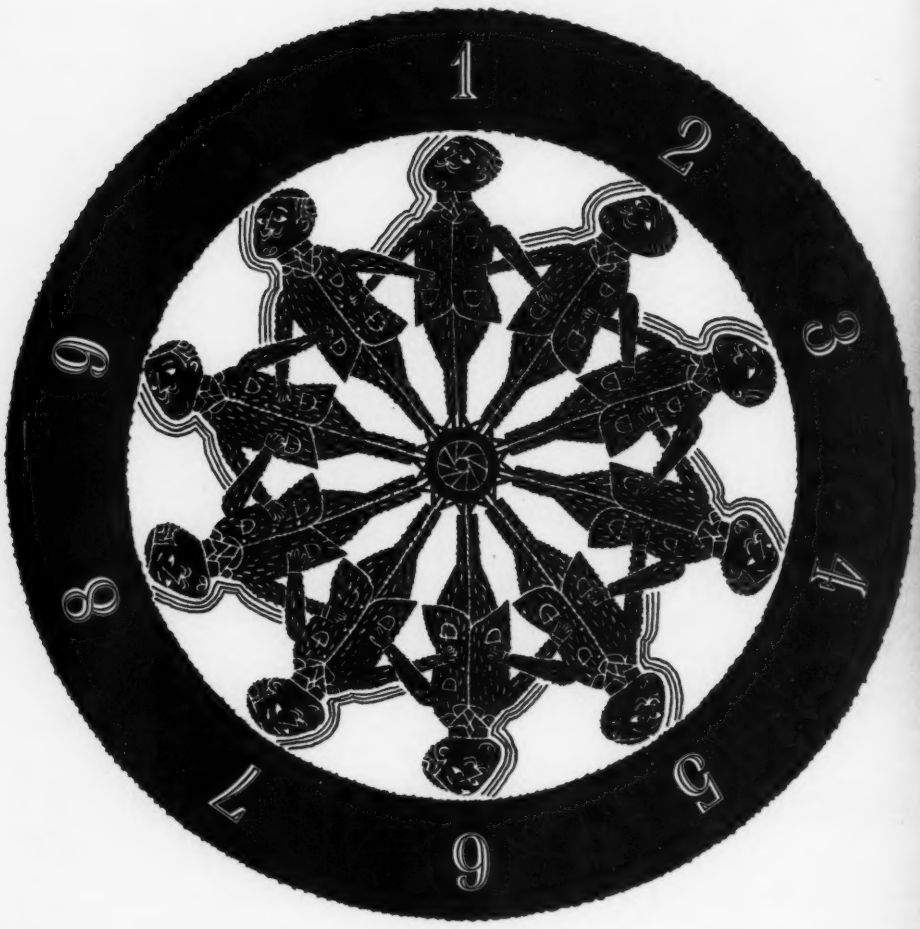
dosage: Therapeutic, 6 to 9 capsules daily, in divided doses. Maintenance, one capsule b.i.d. or t.i.d.

supplied: Bottles of 100, 500 and 1000 capsules.

*Special anti-atherogenic diet sheets for patient distribution and LUFA samples and literature on request.

u. s. vitamin & pharmaceutical corporation
Arlington-Funk Laboratories, division
250 East 43rd Street, New York 17, N. Y.

above: normal arterial lumen
below: extensive narrowing due to cholesterol



Antivert®

STOPS VERTIGO 9 TIMES OUT OF 10!!

The latest ANTIVERT report confirms earlier findings: ANTIVERT relieves vertigo in 9 out of 10 patients. This combination of meclizine (an outstanding antihistamine for vestibular dysfunction) and nicotinic acid (the drug of choice for prompt vasodilation[1]) "... proved more effective than the use of either drug alone."[2] Out of 50 patients with Meniere's syndrome, only 4 failed to respond to ANTIVERT.[2]

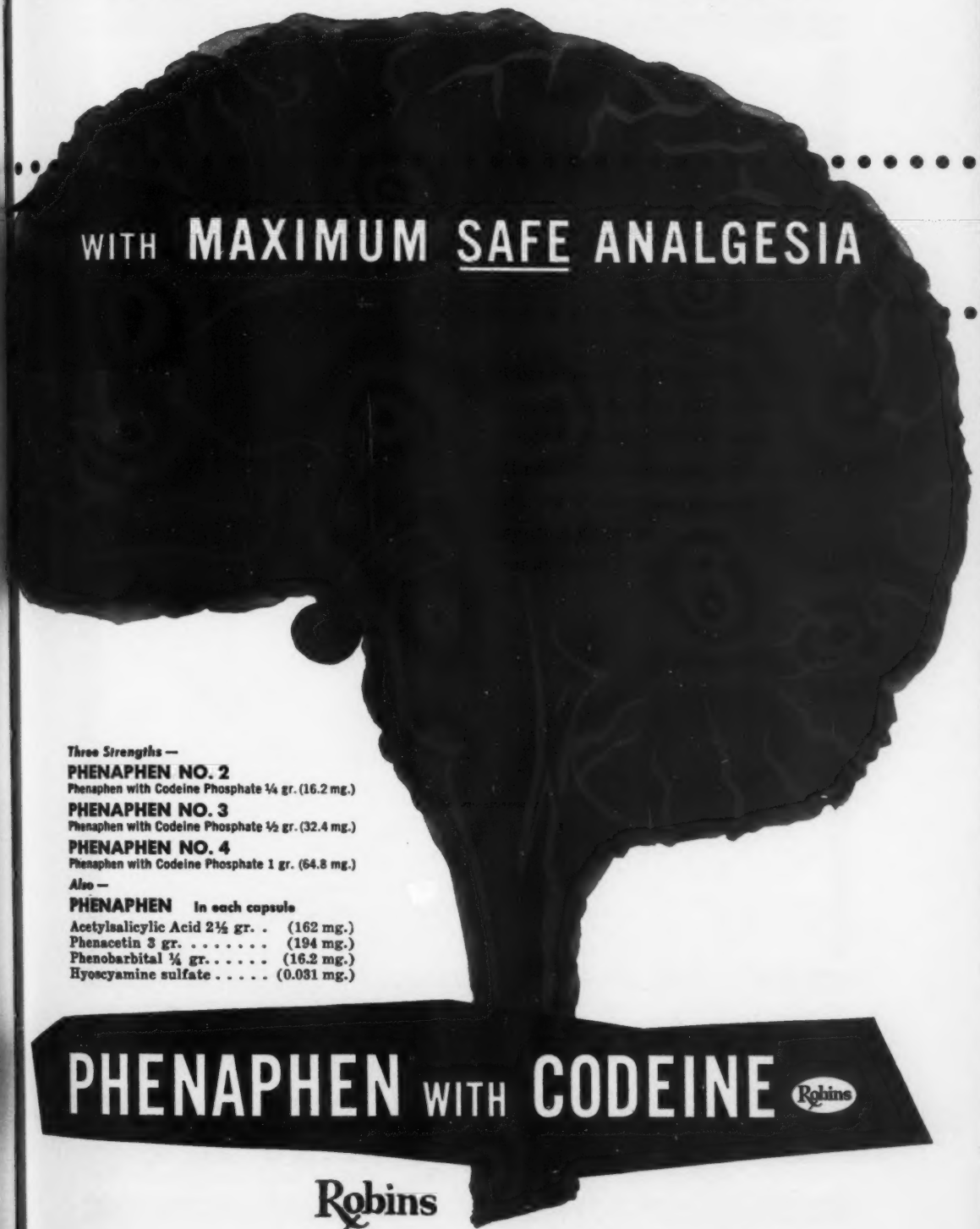
Prescribe one ANTIVERT tablet (12.5 mg. meclizine; 50 mg. nicotinic acid) before each meal for relief of Meniere's syndrome, arteriosclerotic vertigo, labyrinthitis and vertigo of nonspecific origin.

Supplied: In bottles of 100 blue-and-white scored tablets. Prescription only.

References: 1. Menger, H. C.: Clin. Med. 4:313 (Mar.) 1957. 2. Seal, J. C.: Eye Ear Nose & Throat Month. 38:738 (Sept.) 1959.

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

Raise the Pain Threshold



WITH MAXIMUM SAFE ANALGESIA

Three Strengths —

PHENAPHEN NO. 2
Phenaphen with Codeine Phosphate ¼ gr. (16.2 mg.)

PHENAPHEN NO. 3
Phenaphen with Codeine Phosphate ½ gr. (32.4 mg.)

PHENAPHEN NO. 4
Phenaphen with Codeine Phosphate 1 gr. (64.8 mg.)

Also —

PHENAPHEN In each capsule
Acetylsalicylic Acid 2½ gr. . (162 mg.)
Phenacetin 3 gr. . . . . (194 mg.)
Phenobarbital ¼ gr. . . . . (16.2 mg.)
Hyoscyamine sulfate . . . . . (0.031 mg.)

PHENAPHEN WITH CODEINE

Robins

Robins

A. H. ROBINS CO., INC., RICHMOND 20, VIRGINIA

Ethical Pharmaceuticals of Merit since 1878

BEFORE: Severe, persistent dermatomycosis of several months duration.

NOW AVAILABLE
WHITE'S VITAMIN
A & D OINTMENT
with **Prednisolone**

AFTER: Same patient after two weeks therapy with Vitamin A and D Ointment with Prednisolone. Medication applied twice daily.

White's Vitamin A and D Ointment is now available **with Prednisolone** (0.5 per cent) in a lanolin-petrolatum base. The local anti-inflammatory and anti-pruritic effects of prednisolone augment the healing, soothing and protective effects of White's Vitamin A and D Ointment. **For dermatoses caused by thermal or chemical irritants, common allergic skin disorders and nonspecific pruritus ani and vulvae.** Supplied in 10 and 25 Gm. tubes.

White Laboratories, Inc., Kenilworth, New Jersey. White

effective cleansing

MASSENGILL® POWDER

the buffered acid vaginal douche with low surface tension

Surface tension of Massengill Powder in standard solution is 50 dynes/cm., compared to vinegar at 72 dynes/cm. This low surface tension enables Massengill Powder to penetrate and cleanse the folds of the vaginal mucosa. It also makes cell walls of infecting organisms more susceptible to therapy.

Massengill Powder is mildly astringent and soothing to inflamed tissue. Patients like its clean, refreshing odor.

Valuable adjunct in management of monilia, trichomonas, staphylococcus and streptococcus vaginal infections.

contains: Ammonium Alum, Boric Acid, Phenol, Menthol, Berberine, Thymol, Eucalyptol, and Methyl Salicylate.

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee • New York • Kansas City • San Francisco

CRITICAL pH ZONE

The normal vagina has a pH of 3 to 4.5, but an infection usually causes the pH to rise. An alkaline mucosa neutralizes a simple, unbuffered acid douche like vinegar within 30 minutes.

In contrast, the *buffered* acid douche solution of Massengill Powder (pH 3.5 - 4.5) resists neutralizing. The normal, low pH is maintained for 4 to 6 hours in ambulant patients and as long as 24 hours in recumbent patients. This low pH inhibits the propagation of monilia, trichomonas vaginalis, and pathogenic bacteria, but permits growth of the beneficial Döderlein bacillus.

MASSENGILL® POWDER

the buffered acid vaginal douche with low surface tension

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee • New York • Kansas City • San Francisco

make them measure up

Incremin® with iron Syrup

Lysine-Vitamins Lederle

help restore the normal blood picture—iron as ferric pyrophosphate to restore or maintain normal hemoglobin.

boost appetite and energy—vitamins . . . B_1, B_6 and B_{12}.

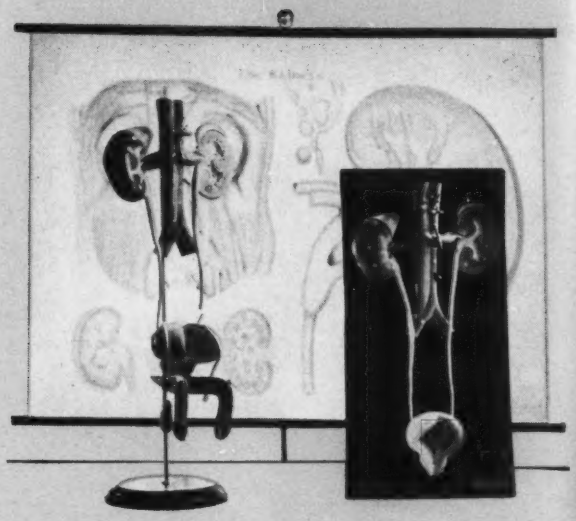
upgrade low-grade protein—cereals and other low protein favorites of children, upgraded by l-Lysine, work with meat and other top protein to build stronger bodies.

tastes good! Each daily cherry-flavored teaspoonful dose (5 cc.) contains:

l-Lysine HCl	300 mg.
Vitamin B_{12} Crystalline	25 mcgm.
Thiamine HCl (B_1)	10 mg.
Pyridoxine HCl (B_6)	5 mg.
Ferric Pyrophosphate (Soluble)	250 mg.
Iron (as Ferric Pyrophosphate)	30 mg.
Sorbitol	3.5 Gm.
Alcohol	0.75%

Bottles of 4 and 16 fl. oz.

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York



in genitourinary tract infections

6,800,000

courses of treatment* and still negligible development of bacterial resistance with

FURADANTIN®

brand of nitrofurantoin

"...may be unique as a wide-spectrum antimicrobial agent that...does not invoke resistant mutants."

Waisbren, B. A., and Crowley, W.: A.M.A. Arch. Int. M. 95:653, 1955.

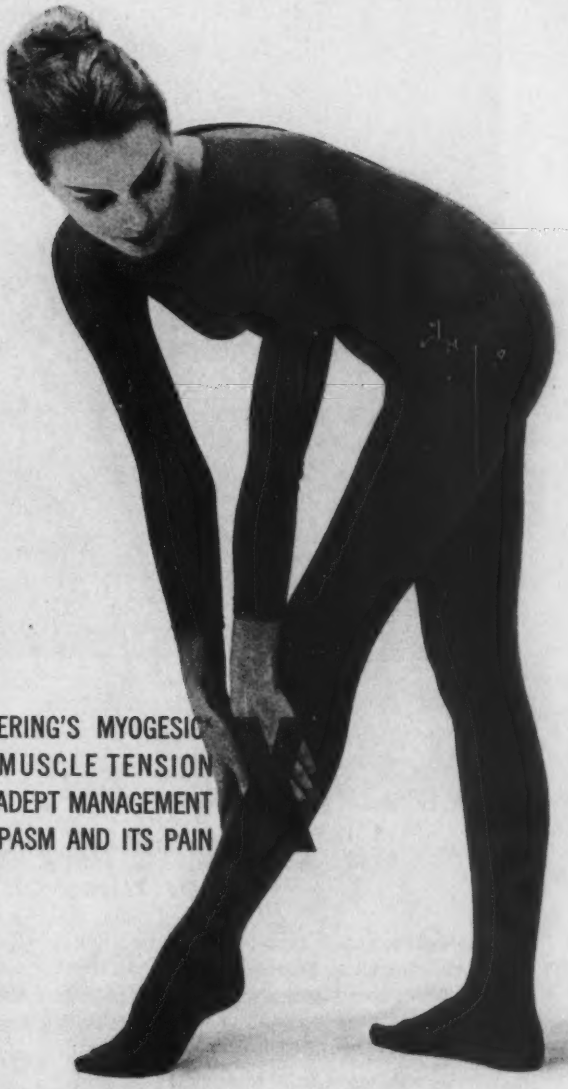
Available as Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

*Conservative estimate based on the clinical use of FURADANTIN Tablets and Oral Suspension since 1953.

Illustration through courtesy of Clay-Adams, Inc., New York

NITROFURANS—a *unique* class of antimicrobials—neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK



NO SPRAIN, NO STRAIN, OR LOW BACK PAIN

can resist the rapid relaxant relief of

RELA™

CARISOPRODOL

RELA—SCHERING'S MYOGESIC
RELAXES MUSCLE TENSION
FOR MORE ADEPT MANAGEMENT
OF BOTH SPASM AND ITS PAIN

Rela is most useful in the areas where narcotic analgesics are unwarranted and where salicylates are inadequate. Its muscle-relaxant properties are dependable yet significantly free of the limitations or problems often associated with other relaxants.

Rela relaxes acute muscle spasm. Relief of muscle spasm (excellent to good effectiveness in the majority of patients).[1]

Rela provides persistent pain relief through its relaxant and analgesic actions. "Relief from pain was usually rapid and sometimes dramatic."[1]

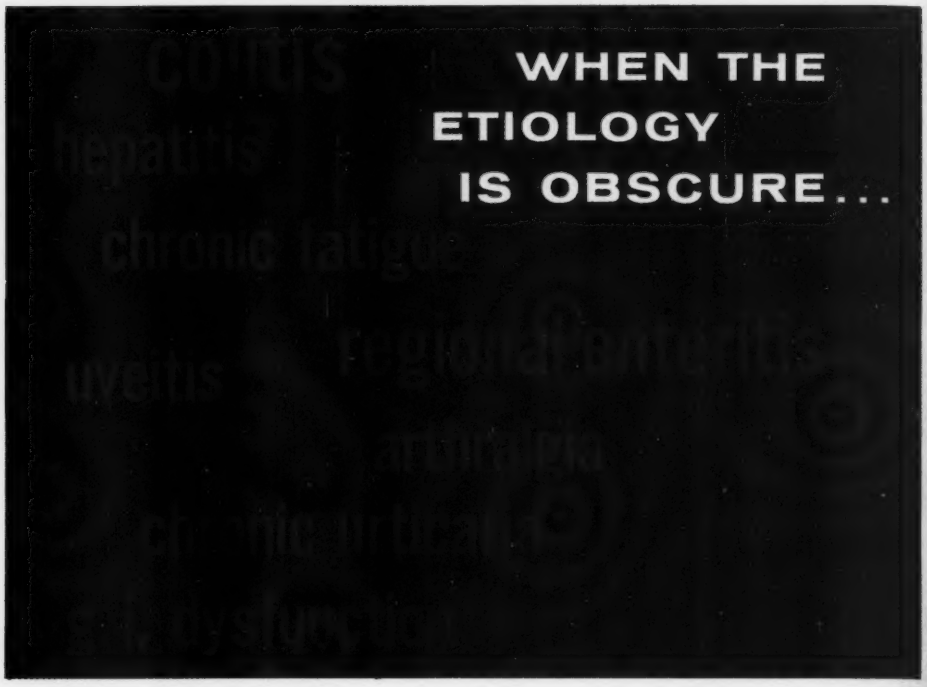
Rela provides comfort free of spasm and pain. "A number of patients reported freedom from insomnia which they attributed to freedom from pain."[1]

Schering

℞ **MYOGESIC:** MUSCLE RELAXANT ANALGESIC

M-283

1. Kuge, T.: To be published.



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MOAN ANTIGEN

definitely establishes the cause or rules out a frequent cause

Amebiasis can cause a multitude of varied, nonspecific symptoms. Because diagnosis has been so difficult, many cases are not detected. Stool examinations are notoriously unreliable, particularly in chronic, extraintestinal amebic infection.[1-8]

Now, after ten years of research, Moan Antigen provides a simple, dependable serologic test for amebiasis.

Rigidly controlled, highly critical studies show that the Moan Test has the two essential qualities of a good serodiagnostic test: *sensitivity* (consistently positive results in clinically significant cases); and *specificity* (consistently negative results in the absence of significant pathology due to amebiasis). Thus the Moan Test definitely establishes *E. histolytica* as the cause of symptoms, or definitely rules it out.[9-12]

The Moan Test is extremely simple to perform. It does not require highly trained personnel or special equipment; it can be done in even the smallest laboratory. When run in quantity, individual tests cost as little as 37c per test.

Write for detailed literature, case histories, and instructions for performing the Moan Test.

1. Webster, B.H.: Am. Pract. and Dig. of Treat., *9*:897 (June, 1958). • 2. D'Antoni, J.S.: Am. J. Trop. Med. and Hyg., *29*:269 (May, 1949). • 3. Rinehart, R.E., and Marcus, H.: Northwest Med., *54*:708 (July, 1955). • 4. Elsdon-Dew, R.: S. Afr. Med., *32*:89 (Jan., 1958). • 5. Cook, J.E., Briggs, G.W., and Hindley, F.W.: Am. Pract. and Dig. of Treat., *6*:1821 (Dec., 1955). • 6. Farfel, B.: Am. J. of Gastroenterology, *32*:620 (Nov., 1959). • 7. Eisert, J., Hannibal, J.E., and Sanders, S.L.: New Eng. J. of Med., *261*:843 (Oct. 22, 1959). • 8. McHardy, G.C.: Gastroenterology, *30*:535 (1956). • 9. Moan, J.C.: Am. J. Trop. Med. and Hyg., *6*:499 (May, 1957). • 10. Babione, R.W., and Moan, J.C.: (to be published). • 11. Babione, R.W.: (to be published). • 12. Perkins, J.G.: U. of Oregon Med. School, Mar. 19-20, 1959.

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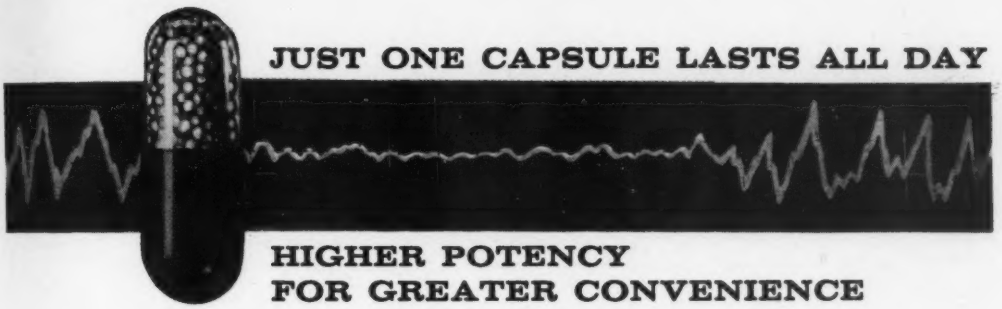
85 N. Lansdowne Ave. Lansdowne, Pa.

NEW AND EXCLUSIVE

FOR SUSTAINED TRANQUILIZATION

MILTOWN® (*meprobamate*) now available
in 400 mg. continuous release capsules as

Meprospan®-400



JUST ONE CAPSULE LASTS ALL DAY

**HIGHER POTENCY
FOR GREATER CONVENIENCE**

- relieves *both* mental and muscular tension without causing depression
- does not impair mental efficiency, motor control, or normal behavior

Usual dosage: One capsule at breakfast, one capsule with evening meal

Available: *Meprospan-400*, each blue capsule contains 400 mg. Miltown (meprobamate)
Meprospan-200, each yellow capsule contains 200 mg. Miltown (meprobamate)
Both potencies in bottles of 30.

WALLACE LABORATORIES, *New Brunswick, N. J.*

CME-9436

Fostex® treats their acne while they wash

completely emulsifies and washes off excess oil from the skin.

penetrates and softens comedones, unblocks pores and facilitates removal of sebum plugs.

removes papule coverings and permits drainage of sebaceous glands.

Patients like Fostex because it is so easy to use. They simply wash acne skin 2 to 4 times a day with Fostex Cream or Fostex Cake, instead of using soap.

Fostex contains Sebulytic®,* a combination of surface-active wetting agents with remarkable antiseborrheic, keratolytic and antibacterial actions . . . enhanced by sulfur 2%, salicylic acid 2%, and hexachlorophene 1%.

*sodium lauryl sulfoacetate, sodium alkyl aryl polyether sulfonate and sodium dioctyl sulfosuccinate.

Fostex is available in two forms—

FOSTEX CREAM, in 4.5 oz. jars.

FOSTEX CAKE, in bar form.

Fostex Cream and Fostex Cake are interchangeable for therapeutic washing of the skin. Fostex Cream is approximately twice as drying as Fostex Cake.

Fostex Cream is also used as a therapeutic shampoo in dandruff and oily scalp.

Write for samples.

WESTWOOD PHARMACEUTICALS • Buffalo 13, New York

Tofrānil®

brand of imipramine HCl

in depression

lights the road to recovery
in 80 per cent of cases

In the treatment of depression Tofrānil has established the remarkable record of producing remission or improvement in approximately 80 per cent of cases.[1-7]

Tofrānil is well tolerated in usage—is adaptable to either office or hospital practice—is administrable by either oral or intramuscular routes.

Tofrānil
a potent thymoleptic . . .
not a MAO inhibitor.

Does act effectively in *all* types of depression regardless of severity or chronicity.

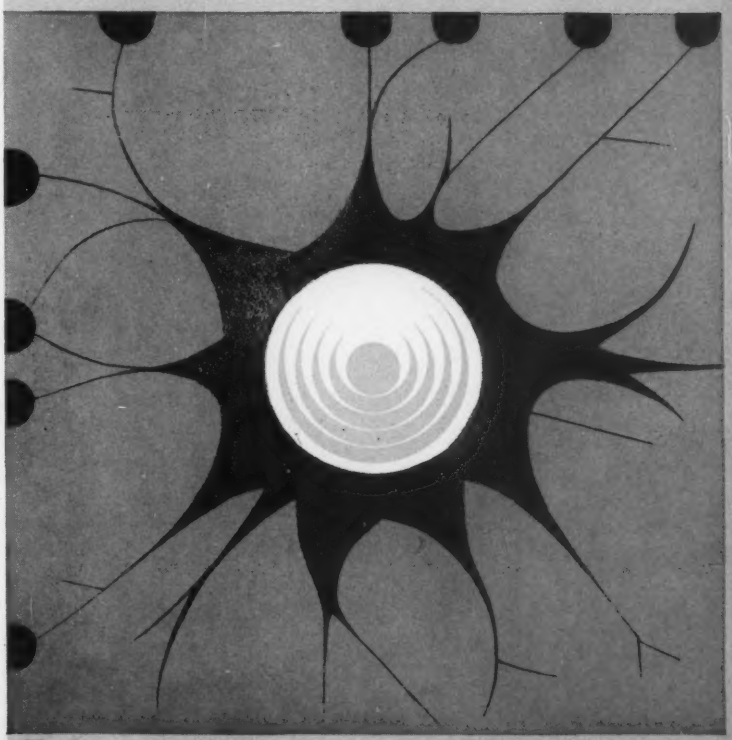
Does not inhibit monoamine oxidase in brain or liver; produce CNS stimulation; or potentiate other drugs such as barbiturates and alcohol.

Detailed Literature Available on Request.

Tofrānil® (brand of imipramine HCl), tablets of 25 mg., bottles of 100. Ampuls for intramuscular administration only, each containing 25 mg. in 2 cc. of solution, cartons of 10 and 50.

References: 1. Ayd, F. J., Jr.: Bull. School Med. Univ. Maryland *44*:29, 1959. 2. Azima, H., and Vispo, R. H.: A. M. A. Arch. Neurol. & Psychiat. *81*:658, 1959. 3. Lehmann, H. E.; Cahn, C. H., and de Verteuil, R. L.: Canad. Psychiat. A. J. *3*:155, 1958. 4. Mann, A. M., and MacPherson, A. S.: Canad. Psychiat. A. J. *4*:38, 1959. 5. Sloane, R. B.; Habib, A., and Batt, U. E.: Canad. M. A. J. *80*:540, 1959. 6. Straker, M.: Canad. M. A. J. *80*:546, 1959. 7. Strauss, H.: New York J. Med. *59*:2906, 1959.

Geigy, Ardsley, New York



Geigy

TO 4-60

Now—All cold symptoms can be controlled

Tussagesic

timed-release tablets

Controls congestion
with Triaminic,[1,2,3] the leading oral nasal decongestant.

Controls aches and fever
with well-tolerated APAP, non-addictive analgetic[4] and excellent antipyretic.[5]

Each TUSSAGESIC Tablet provides:

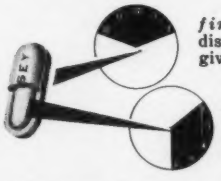
TRIAMINIC® .....50 mg.
(phenylpropanolamine HCl .....25 mg.
pheniramine maleate .....12.5 mg.
pyrilamine maleate .....12.5 mg.)
Dormethan
(brand of dextromethorphan HBr)..... 30 mg.
Terpin hydrate .....180 mg.
APAP (N-acetyl-p-aminophenol) .....325 mg.

References: 1. Lhotka, F. M.: Illinois M. J. 112:259 (Dec.) 1957. 2. Fabricant, N. D.: E.E.N.T. Monthly 37:460 (July) 1958. 3. Farmer, D. F.: Clin. Med. 5:1183 (Sept.) 1958. 4. Bonica, J. J.: in Drugs of Choice, Mosby, St. Louis, 1958, p. 272. 5. Dascomb, H. E.: in Current Therapy, Saunders, Phila., 1958, p.78. 6. Bickerman, H. A.: in Drugs of Choice, Mosby, St. Louis, 1958, p.547.

Controls cough centrally
with non-narcotic Dormethan, possessing "amply demonstrated" antitussive activity,[6] as effective as codeine.

Liquefies tenacious mucus
with terpin hydrate, classic expectorant.

Prompt and prolonged relief because of this special "timed release" design:



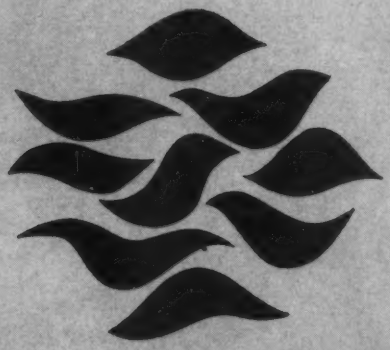
first – the outer layer dissolves within minutes to give 3 to 4 hours of relief

then – the inner core releases its ingredients to sustain relief for 3 to 4 more hours

Dosage: One tablet in the morning, midafternoon and at bedtime. Pediatric dosage chart for Tussagesic Suspension available on request.

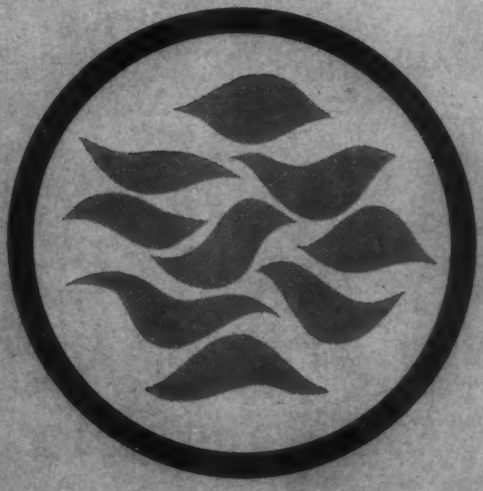
TUSSAGESIC SUSPENSION provides palatability and convenience which make it especially attractive to children and other patients who prefer liquid medication.

SMITH-DORSEY • a division of The Wander Company • Lincoln, Nebraska



in eight years Novahistine hasn't cured a single cold—but it has brought

prompt relief of symptoms to almost 8,000,000 patients*



With the introduction of Novahistine, a better and safer way to relieve symptoms of a cold became available to physicians. The synergistic action of the Novahistine formula...combining an orally-effective vasoconstrictor with an antihistamine...promptly clears the air passages and checks irritant nasal secretions. NOVAHISTINE can eliminate the problem of rebound congestion and damage to nasal mucosa in patients who misuse topical applications. • For long-lasting "Novahistine Effect" prescribe Novahistine LP Tablets...which begin releasing medication as promptly as conventional tablets but continue bringing relief for 8 to 12 hours. Two Novahistine LP Tablets in the morning and two in the evening will effectively control the average patient's discomfort from a cold. Each tablet contains phenylephrine HCl, 20 mg., and chlorprophenpyridamine maleate, 4 mg.

*Based on National Prescription Audits of new Novahistine prescriptions since 1952.

PITMAN-MOORE COMPANY Division of Allied Laboratories, Inc. • Indianapolis 6, Indiana

Novahistine LP†

LONG-ACTING

†Trademark

BAD DIGESTION INCLINES ONE TO SKEPTICISM, INCREDULITY, BREEDS BLACK FANCIES AND THOUGHTS OF DEATH JOSEPH CONRAD

When bad digestion is the consequence of digestive enzyme deficiency, Entozyme may dispel dreary symptoms such as pyrosis, flatulence, belching, and nausea, for it is a natural supplement to digestive enzymes. It provides components with digestive enzyme activity: **Pepsin,** N. F., 250 mg., **Pancreatin,** F., 300 mg., and **Bile Salts,** 150 mg. Because Entozyme is actually a tablet-within-a-tablet, these components are freed in the physiological areas where they occur naturally. Entozyme has proved useful in relieving many symptoms associated with cholecystitis, post-cholecystectomy syndrome, sub-total gastrectomy, pancreatitis, infectious hepatitis, and a variety of metabolic diseases.

A. H. ROBINS CO., INC. • RICHMOND 20, VA.

ENTOZYME

in low back pain, arthritis and other musculoskeletal disorders...

Analexin is the only drug known to produce both general analgesia and muscle relaxation. It is effective in a wide variety of acute and chronic conditions where both pain and muscle tension may be involved, such as: low back pain, sprains and strains, myalgia, arthritis, osteoarthritis.

In various clinical trials where Analexin was used for relief of pain, satisfactory analgesia has resulted in up to 70% of patients with musculoskeletal disorders. These patients comprising ". . . one of our largest clinical problems of moderately severe painful states . . ."[5] require continuous satisfactory relief without tolerance, cumulative toxicity or serious side effects.

TYPICAL RESULTS WITH ANALEXIN* AND ANALEXIN-AF IN MUSCULOSKELETAL ASSOCIATED PAIN[6]

Indications	No. Patients	Relief	Slight or no relief
pain associated with:			
acute, chronic and traumatic musculoskeletal disorders	30	25	5
myositis, myalgia and tendinitis	26	22	4
osteoarthritis	82	62	20
rheumatoid arthritis	38	23	15
arthralgia	15	9	6
Totals	191	141	50

*Generically designated as phenyramidol HCl in clinical trials.

Analexin satisfies ". . . the majority of the criteria demanded of a moderately potent non-specific analgesic agent. There is no question that the predictability of satisfactory control of a paintful state is high and the occurrence of untoward reactions is low."[7]

Batterman, Grossman and Mouratoff[5] reported on the effectiveness of phenyramidol (Analexin) as compared with aspirin, sodium salicylate, and a placebo. They found that even at low dosage phenyramidol produced satisfactory analgesia in more than half of the patients; and when the dose was increased, six out of ten patients were relieved of pain in musculoskeletal disorders with no increase in the incidence of side effects. They conclude ". . . in contrast to codeine and meperidine, the likelihood of untoward reactions occurring in ambulant patients is not high. This is a decided advantage since the control of pain in the ambulant patient with chronic pain is a major clinical problem."

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Squibb Announces Chemipen

Squibb Alpha-Phenoxyethyl Penicillin Potassium

new chemically improved penicillin which provides the highest blood levels that are obtainable with oral penicillin therapy

As a pioneer and leader in penicillin therapy for more than a decade, Squibb is pleased to make Chemipen, a new chemically improved oral penicillin, available for clinical use.

With Chemipen it becomes possible as well as convenient for the physician to achieve and maintain higher blood levels—with greater speed—than those produced with comparable therapeutic doses of potassium penicillin V. In fact, Chemipen is shown to have a 2:1 superiority in producing peak blood levels over potassium penicillin V.*

Extreme solubility may contribute to the higher blood levels that are so notable with Chemipen.* Equally notable is the remarkable resistance to acid decomposition (Chemipen is stable at 37°C. at pH 2 to pH 3), which in turn makes possible the convenience of oral treatment.

And the economy for your patients will be of particular interest—Chemipen costs no more than comparable penicillin V preparations.

Dosage: Doses of 125 mg. (200,000 u.) or 250 mg. (400,000 u.), t.i.d., depending on the severity of the infection. The usual precautions must be carefully observed with Chemipen, as with all penicillins. Detailed information is available on request from the Professional Service Department.

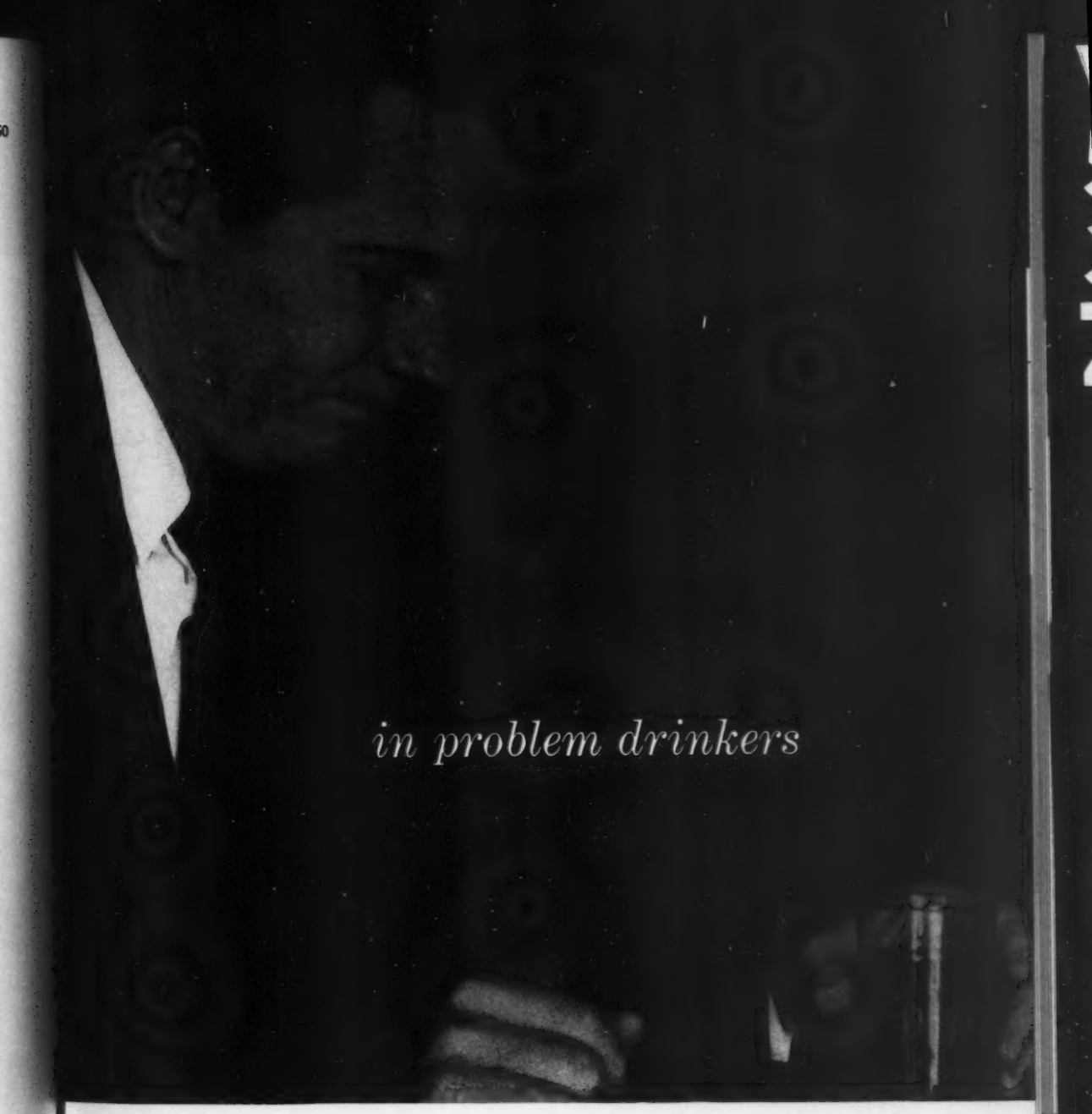
Supply: Chemipen Tablets of 125 mg. (200,000 u.) and 250 mg. (400,000 u.), bottles of 24 tablets. Chemipen Syrup (cherry-mint flavored, nonalcoholic), 125 mg. per 5 cc., 60 cc. bottles.

SQUIBB

Squibb Quality—the Priceless Ingredient

*Knudsen, E. T., and Rolinson, G. N.: Lancet 2:1105 (Dec. 19) 1959.

"CHEMIPEN" IS A SQUIBB TRADEMARK.



Vistaril®

hydroxyzine pamoate

dispels tension...
maintains tranquility

When tension and anxiety "drive him to drink," the problem drinker often finds that VISTARIL, by maintaining tranquility, restores perspective and helps him accept counsel more readily.

VISTARIL has demonstrated a wide margin of safety even in large doses (300-400 mg. daily) over prolonged periods. Clinical studies of alcoholism have shown that VISTARIL produces no significant depression of blood pressure, pulse rate, or respiration in chronic drinkers.

Capsules—25, 50, and 100 mg. *Parenteral Solution* (as the HCl)—25 mg. per cc., 10 cc. vials and 2 cc. Steraject® Cartridges; 50 mg. per cc., 2 cc. ampules.

Professional literature available on request from the Medical Department, Pfizer Laboratories, Div., Chas. Pfizer & Co., Inc., Brooklyn 6, New York

Pfizer *Science for the world's well-being™*

for your depressed dieters...

DEXAMYL® **Spansule® capsules**
Tablets · Elixir
brand of dextro amphetamine and amobarbital

In overweight, 'Dexamyl' helps your patients stick to their diets by

1. overcoming the depression which so often causes overeating

2. relieving the nervousness and irritability so frequently caused by strict reducing regimens

When listlessness and lethargy are problems in reducing, your patients will often benefit from the gentle stimulating effect of

DEXEDRINE® Spansule® capsules · Tablets · Elixir
brand of dextro amphetamine

SMITH
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RESULTS IN 366 PATIENTS WITH STOMACH ULCERS

DIAGNOSIS	TOTAL	MARKED IMPROVEMENT WITH X-RAY GAINS	MARKED IMPROVEMENT	SLIGHT IMPROVEMENT	NO IMPROVEMENT
PEPTIC	50	10	29	9	2
GASTRIC	56	11	33	10	2
DUODENAL	256	39	175	33	9
PYLORIC	4	—	1	2	1
TOTAL	366	60	238	54	14
Summary of investigators' reports.		16%	65%	15%	4%

REPORTED BY PATIENTS, CONFIRMED BY X-RAY, 81% MARKED IMPROVEMENT IN STOMACH ULCER.

proven relief of pain, spasm and nervous tension without the side effects of belladonna, bromides or barbiturates

INDICATIONS—

duodenal and gastric ulcer
gastritis
colitis
spastic and irritable colon
gastric hypermotility
esophageal spasm
intestinal colic
functional diarrhea
G. I. symptoms of anxiety states

NOW—2 FORMS
for adjustability of dosage

Milpath - 400—Yellow, scored tablets of 400 mg. meprobamate and 25 mg. tridihexethyl chloride (formerly supplied as the iodide). Bottle of 50.

Dosage: 1 tablet t.i.d. at mealtime and 2 at bedtime.

Milpath - 200—Yellow, coated tablets of 200 mg. meprobamate and 25 mg. tridihexethyl chloride. Bottle of 50.

Dosage: 1 or 2 tablets t.i.d. at mealtime and 2 at bedtime.

Milpath®

®Miltown + *anticholinergic*

WALLACE LABORATORIES *New Brunswick, N. J.*

813

Lutrexin®

(H. W. & D. brand of lututrin) TABLETS

LUTREXIN has been used successfully in dysmenorrhea[1,2] for the past six years, as well as in premature labor[3,4] and threatened and habitual abortion[5,6].

LUTREXIN exerts an indirect, as well as a direct, relaxing action on the uterus by blocking the pituitary hormones.[7]

LUTREXIN administered orally decreases uterine contractions within thirty minutes.

LUTREXIN is a naturally occurring, non-steroid, uterine relaxing hormone, biochemically different from other ovarian hormones.

1. *Jones, G. S. and Smith, F.: Am. J. Obstet. Gynecol., Vol. 67, No. 3, 628-633, 1954.*
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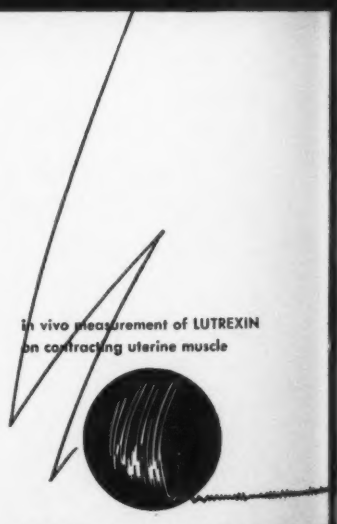

In vivo measurement of LUTREXIN on contracting uterine muscle

HYNSON, WESTCOTT & DUNNING, INC.

BALTIMORE 1, MARYLAND

Southern Medical Journal

PUBLISHED BY SOUTHERN MEDICAL ASSOCIATION

April 1960

The Symposium on Nuclear Medicine

Chairman's Address*

J. R. MAXFIELD, JR., M.D., *Dallas, Tex.*

THIS PROGRAM is an innovation at this Southern Medical Association Session. The Committee believes that it will establish an important phase of medicine as an integral part of the program of the Southern Medical Association. The speakers assembled are outstanding. The quality of the presentations will be in keeping with the aims of the Southern Medical Association. This forward look in modern medicine bespeaks the awareness of your Councilors to bring to the membership of the Southern Medical Association the most advanced medical achievements. This Symposium is being held at the same time as the Symposium on Geriatrics. These two, the new and the old, are the great fields in the future of medicine.

Radioactive technics have frequently been ranked with the microscope in importance to biology and medicine. They furnish valuable means of gaining knowledge about body processes. Hundreds of hospitals now consider them as a part of their regular armamentarium. About 1,900 medical institutions and private practicing physicians have been licensed to use radioactive isotopes. Over a million investigations and treatments of patients per year are being carried out by the use of radioactive isotope technics. This is truly a field of the present as well as the future.

This Symposium will present these basic aspects of radioisotopes in Nuclear Medicine: (1) medical and biologic research; (2) medical diagnosis; (3) medical treatment; and (4) protection to the public.

*Chairman's Introductory Remarks, Symposium on Nuclear Medicine, Southern Medical Association, Fifty-Third Annual Meeting, Atlanta, Ga., November 16-19, 1959.

Address of Welcome*

GENERAL GEORGE J. HEARN, *Atlanta, Ga.*

DR. MAXFIELD and other distinguished delegates to the Symposium on Nuclear Medicine. It is a genuine pleasure and a privilege for me to appear here this morning to welcome you to the State of Georgia on behalf of Governor Ernest Vandiver. Unfortunately, Governor Vandiver could not arrange his schedule to be with you today, but I can assure you that he is wholeheartedly behind your great organization in your search for new and revolutionary medication through the use of nuclear energy.

I am sure I express Governor Vandiver's sentiments when I say that this important Symposium on Nuclear Medicine represents

*Address of Welcome, read before the Symposium on Nuclear Medicine, Southern Medical Association, Fifty-Third Annual Meeting, Atlanta, Ga., November 16-19, 1959.

one of the greatest public service endeavors attempted in this field. You are studying a new and challenging science, one from which all mankind will benefit.

As you may know, Governor Vandiver is a member of The Nuclear Energy Committee of the Southern Governors' Conference and made a recent report to the Southern Governors in support of the Southern Interstate Nuclear Compact. It is his belief that the compact will be able to "provide us with the best possible technical advice in this new and stimulating field."

Georgia is honored to have such dedicated scientists within her borders for this vital study on nuclear medicine. It is encouraging to all our citizens that men of your high caliber have undertaken this unremitting fight for the good of the public's health.

Our Southeastern section of the nation is progressing at a greater rate than at any time in its history, and Georgia is happy to share in this advancement with other states in the area represented at this Symposium.

It is with a high degree of pride and appreciation that I acknowledge your vital contributions to the public welfare. Your deliberations here will be a source of great comfort to all who look to the future in hope of cures that have defied modern medicine.

Again, I welcome you in behalf of the Governor of the State of Georgia.

Some Fundamentals of Radiologic Physics*

THOMAS G. MITCHELL, Lt., MSC, USN,† *Bethesda, Md.*

Introduction

A KNOWLEDGE of the physical fundamentals of radioactive isotopes of the elements is necessary for all practicing physicians today, whether they intend to use radioactive isotopes in their own practice directly, to refer patients to others for diagnostic tests and/or therapy involving radioactive materials, or to counsel patients who bring to the practitioner questions concerning these materials. Radioactive elements, as you know, were discovered and isolated over 60 years ago by the Curies, who first extracted polonium, and then radium, from the ore pitchblende. Radium therapy by implantation in tissue was, and still is, a widely used form of radiation therapy. In addition to radium, several other elements existing in nature have radioactivity associated with them. Of more than academic interest to us is the radiation in our environment from carbon-14 (C^{14}) and potassium-40 (K^{40}), both of which contribute to the background radiation to which we are constantly exposed.

Artificially produced radioactive isotopes of the elements began to appear in the 1930's following the development of the cyclotron, a particle accelerator, previously referred to as an "atom smasher," which found great use in exploring the nature of the atom by bombarding suitable targets with high speed particles. The supply of radionuclides (a general term which is used to include all radioactive isotopes of the elements) from such sources was only a trickle compared to the amount which became available after 1946, when some nuclear reactors were diverted from their wartime applications and turned to the production of radionuclides useful in industry, research and medicine.

If we consider for a moment a currently acceptable model for the atom, we see that it consists of an extremely dense, small kernel or nucleus, with one or more electrons revolving about it in much the same way that the planets revolve about the sun. However, these electrons revolve in all different planes, unlike the planets. The nucleus is made up of

*Read before the Symposium on Nuclear Medicine, Southern Medical Association, Fifty-Third Annual Meeting, Atlanta, Ga., November 16-19, 1959.

†From the U. S. Naval Hospital, National Naval Medical Center, Bethesda, Md.

The opinions or assertions contained herein are the private ones of the author and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

elementary particles, among which are protons which are positively charged, and neutrons which, as their name implies, carry no electric charge. (The most common isotope of hydrogen has no neutrons in its nucleus.) In the neutral atom the electric charge of the nucleus is always balanced by the charge of the electrons which, in the neutral atom, are numerically equal to the number of protons in the nucleus. A positive ion is an atom which has a deficit of electrons, while a negative ion is an atom which has an excess of electrons. The chemical properties of atoms are determined by the number of electrons in the atom, and therefore ultimately by the number of protons in the nucleus. Chemical reactions are mediated through the outermost or valence electrons. The energies involved in chemical reactions which affect these outer electrons only are of the order of 5 to 15 electron volts per atom. The electron volt is a very small unit of energy, which is defined as the energy acquired by an electron when it is accelerated across a potential difference of one volt.

$$C + 2O \rightarrow CO_2 + Q$$
$$Q = 4 \text{ electron volts}$$

Energies involved in nuclear reactions are much greater by comparison.

$$C^{14} \rightarrow N^{14} + {}_{-1}e^{0} + Q$$
$$Q = 155{,}000 \text{ electron volts}$$

Electrons have very little mass, their contribution to the total mass of the atom being almost negligible. An electron has a mass of about 9×10^{-28} grams, or about one eighteen-hundredth of the mass of a proton or neutron. The diameter of the nucleus is of the order of 10^{-12} cm., while the atom has an effective diameter of about 10^{-8} cm., or one angstrom unit. The great majority of the atom's mass is concentrated in the nucleus which, due to its small size, has a density of astronomic proportions, over a trillion times that of lead.

If we compared the size of the nucleus to a golf ball, the atom would be about the size of a football stadium. These dimensions show the very small probability of making a direct hit on a nucleus with projectiles fired at it.

Atoms are classified according to the number of protons in the nucleus, which number is equal to the number of electrons in the neutral atom. The number of protons is referred to as the atomic number, which is characteristic of an element. The atomic number is referred to as the Z-number, and in shorthand notation is written as a subscript to the left of the chemical symbol for the element. The mass number, which may differ for atoms of the same element, is equal to the sum of the number of protons and neutrons in the nucleus. Protons and neutrons are collectively called nucleons. The mass number, referred to as the A-number, is written to the right, as a superscript of the chemical symbol, e.g.,

A	23	31
Sym	Na	P
Z	11	15

All atoms of sodium existing in nature have 11 protons and 12 neutrons, yielding a mass number of twenty-three. All atoms of phosphorus existing in nature have 15 protons and 16 neutrons, for a total of 31 nucleons.

Atoms of most of the other elements exist in several different forms in nature. For example, hydrogen exists in the form of ${}_1H^1$ and ${}_1H^2$. These atoms of hydrogen, having different mass numbers, are called isotopes of the element hydrogen. Oxygen has three naturally occurring isotopes, O^{16}, O^{17}, and O^{18}. The existence of isotopes of an element and their relative abundance in nature accounts for the fact that chemical atomic weights are not whole numbers, except in the case of oxygen, which was chosen as the reference. Chlorine for example, has an atomic weight of 35.45. Chlorine exists in nature in the form of Cl^{35} (75% abundance) and Cl^{37} (25% abundance).

A radioactive isotope of an element may be artificially produced in several ways. One method involves a change brought about by introduction of a particle, such as a neutron, or proton, into the nucleus. Another common method is to split an atom such as uranium-235 (U^{235}) into two smaller atoms, both of which are usually radioactive. Examples of the first type production would be:

1. ${}_{14}Si^{30} + {}_1D^2 \rightarrow {}_{15}P^{32}$
2. ${}_{15}P^{31} + {}_0n^1 \rightarrow {}_{15}P^{32}$

You will notice in case 1, that the product, phosphorus-32 (P^{32}), is chemically different from the target material, silicon. P^{32} produced in such a fashion is said to be carrier-free, i.e., it is free from all nonradioactive atoms of phosphorus. In the second case the product

formed is chemically identical with the target material. This product is not carrier-free, and its specific activity depends on the neutron flux to which it was exposed, and the duration of exposure. Specific activity is a ratio which expresses the amount of radioactive isotope present in a sample as a function of the amount of the element present. It is generally expressed as atoms decaying per atoms of the element present.

Fission of U^{235} yields products which comprise many different elements. Chemical separation of these must be carried out, and in many cases it is possible to obtain carrier-free radionuclides. This is the principal source of iodine-131 (I^{131}). One possible reaction forming I^{131} would be:

$$_{92}U^{235} + {}_{0}n^{1} \rightarrow {}_{50}Sn^{131} + {}_{42}Mo^{102} + 3{}_{0}n^{1}$$

In a series of beta decays, tin-131 (Sn^{131}) is ultimately converted to I^{131}, which is then separated chemically from the rest of the fission products.

$$_{50}Sn^{131} \xrightarrow{\beta^-} {}_{51}Sb^{131} \xrightarrow{\beta^-} {}_{52}Te^{131} \xrightarrow{\beta^-} {}_{53}I^{131}$$

The method of production determines the cost and availability of radioactive isotopes. Irradiation with charged particles in particle accelerators is the only practical way of producing some radionuclides such as manganese-54 (Mn^{54}), cobalt-58 (Co^{58}), and arsenic-74 (As^{74}). This method of production yields radionuclides of high specific activity. It is the most feasible method of producing positron emitting radionuclides. The high cost, limited production facilities and relatively low yield are the principal disadvantages to use of this method of production.

Neutron generators such as Polonium-Beryllium sources, Van de Graaff generators, etc., offer a means of producing radionuclides for laboratory demonstrations and limited investigations, but are not suitable for production of radionuclides for clinical use since the neutron flux associated with these sources is low, and therefore the specific activity will also be low.

Nuclear reactors are the greatest controlled sources of neutrons available and are the principal source of the most commonly used radionuclides. Production of P^{32} from P^{31} placed in the reactor for neutron bombardment is an example of the use of a nuclear reactor as a neutron source. Periodic refining of the reactor fuel, uranium, is the usual mode of production of many other radionuclides such as strontium-90 (Sr^{90}), iodine-131 (I^{131}), and cesium-137 (Cs^{137}). Since radionuclides are formed by fission of U^{235}, and are a by-product of nuclear reactor operation, this is the cheapest source of radionuclides.

Radioactive Isotopes

Radioactive isotopes are, as their name implies, atoms of an element distinguishable by their mass. Of far more significance to us is a unique property which they exhibit, of spontaneously giving off excess energy in the form of high speed particles and/or electromagnetic radiation. There are several different modes of decay exhibited by radionuclides. The mode or modes of decay exhibited by any radionuclide is constant for that nuclide. The combination of particles and/or electromagnetic radiations, their energy, and the probability of decay is unique for any radionuclide. One of the ways by which a radionuclide may be identified is by determination of these characteristic properties.

Modes of Decay

Alpha particle emission.

Many naturally radioactive materials emit alpha radiation.* Polonium, the first radioactive element discovered, has an isotope, polonium-210 (Po^{210}), which decays by alpha particle emission.

$$_{84}Po^{210} \rightarrow {}_{82}Pb^{206} + {}_{2}He^{4} + Q$$

Notice that we must balance the equation just as in writing chemical equations, the symbol on the right, Q, indicates that the reaction is exothermal. The energy of the reaction is shared by the resulting atom of lead and the alpha particle. In this case, the alpha particle has an energy of 5.3 million electron volts. Alpha particles have very short ranges in matter, up to only several microns in water. The use of alpha radiation is extremely limited in clinical medicine, although alpha emitters, such as radium, radon, and their daughter products do find use. These nuclides are most often used as sealed gamma ray sources, and the alpha radiation does not penetrate the capsule or other container. Due to their

*The alpha particle is symbolized by α or $_{2}He^{4}$, since it is identical with the nucleus of helium.

high energy, short range, and double positive charge, alpha particles have a very high specific ionization, producing as many as 20,000 ion pairs per cm. path length in air. This, coupled with the fact that most alpha emitters are bone seekers, makes them undesirable for administration other than in sealed containers. Alpha radiation from a radionuclide is often followed by gamma radiation resulting from further rearrangement of nuclear constituents.

$$RaC \rightarrow RaC' + {}_2He^4 + \text{gamma rays}$$

Beta particle emission.

Emission of beta particles results from internal rearrangement and change of the nature of nuclear constituents. The end product is an atom of a different element, with atomic number increased by 1 unit from the parent, mass number remaining the same.

$${}_{15}P^{32} \rightarrow {}_{-1}e^0 + {}_{16}S^{32} + Q$$

Emission of beta particles in some cases may be followed by gamma radiation due to further rearrangement of nuclear constituents.

$${}_{13}Al^{28} \rightarrow {}_{14}Si^{28} + {}_{-1}e^0 + \text{gamma} + Q$$

Beta particles have ranges up to 2.7 cm. in water, although the ones most commonly used clinically have ranges somewhat less than this, e.g., beta particles from yttrium-90 (Y^{90}) have a maximum range of 11 mm., beta particles from phosphorus-32 (P^{32}) have a range of 8 mm., and beta particles from sulfur-35 (S^{35}) have a range of only about 0.2 mm. water. Beta particles exhibit specific ionization much less than that of alpha particles, of the order of 100 ion pairs per cm. path length in air. Many beta particles can easily be detected by inexpensive instruments for radiation detection such as Geiger-Müller counter tubes. Assay of beta emitting radionuclides may be accomplished by counting the beta particles given off per unit time.

Positron emission is a type of radioactive decay which is common to no naturally occurring radionuclide, i.e., it is found only in radionuclides which are artificially produced. It is most often found as a mode of decay in those radionuclides which have less neutrons than the naturally occurring isotopes of that element, e.g., P^{30} is a positron emitter. It has only 15 neutrons in the nucleus, compared to 16 neutrons in the nucleus of P^{31}, the only naturally occurring isotope of phosphorus. Positron emitters are most often produced in particle accelerators such as cyclotrons by bombarding suitable targets with positively charged particles such as protons or deuterons.

$${}_{32}Ge^{73} + {}_1D^2 \rightarrow {}_{33}As^{74} + {}_0n^1$$

The properties of positrons are, for all practical purposes, the same as those of beta particles, since they differ only in charge. The range and specific ionization of a positron would be just about the same as the range and specific ionization of a beta particle of the same energy. Like alpha and beta decay, positron emission may be followed by gamma rays. In addition to such gamma rays, if present, or even in their absence, there is always electromagnetic radiation resulting from the annihilation of a positron-electron pair. This results whenever the positron loses most of its energy by ionization, and is in the process of being "neutralized" by an electron in the medium through which the positron is traveling. Annihilation radiation consists of two photons or quanta of electromagnetic radiation, which are given off simultaneously, 180 degrees apart.

$${}_{+1}e^0 + {}_{-1}e^0 \rightarrow 2 \text{ photons of .51 Mev each}$$

The energy of each of these photons is 0.51 Mev, the energy equivalent of the mass contained in 1 electron according to the classical Einstein equation: $E = mc^2$, where E is in ergs, if m is in grams, and c is the velocity of light in cm. per second. The simultaneous detection of these photons enables one to determine very precisely the position of such a positron emitting source, and finds use today in *in vivo* counting apparatus such as the coincident positron scanner.

Gamma rays.

Gamma rays are a form of electromagnetic radiation which arise from the nuclei of atoms. They have no electrical charge, no rest mass, and travel with the velocity of light in a vacuum. The energy and number of gamma rays per atom disintegrating is a characteristic of a particular radionuclide. Gamma rays interact with matter primarily by imparting all or part of their energy to electrons in the medium through which they are passing. These secondary electrons in turn produce ionization in the medium much the same as a beta particle does. For this reason the specific

ionization of gamma rays is found to be similar to that for beta particles. However, the probability of a gamma ray interacting with an electron is very small. So small, in fact, that we cannot define a range for gamma rays, but must use some other measure to give an indication of their penetrability. This measure is the half-thickness, the thickness of an absorber sufficient to reduce an incident beam of gamma radiation to one half its original intensity. The half-thickness of an absorber for gamma radiation depends on the atomic number of the absorber, the density of the absorber, and the energy of the gamma radiation. In the range of gamma ray energies encountered in the clinical use of radioactive isotopes, the half-thickness of lead for gamma rays varies from e.g., 2 mm. in the case of gamma rays from chromium-51 (Cr^{51}), up to 12 mm. in the case of gamma rays from cobalt-60 (Co^{60}).

Gamma rays, due to their penetrability, may be detected from gamma emitting radionuclides located within the body. This is taken advantage of in the 24 hour thyroid I^{131} uptake studies, scanning for brain tumors, cardiac output studies, etc. As might be expected, there is no difference between the properties of x- and gamma rays. X-rays differ from gamma rays only in point of origin.

One other mode of decay is that of electron capture. A nuclide deficient in neutrons can economically rearrange its nuclear constituents by capturing an electron from one of the inner orbits, such as the K or L orbit. When capture of an electron from the K orbit or shell occurs, it is called K capture, when the electron comes from the L shell, it is called L capture. Electron capture may or may not be followed by gamma radiation, but it is always followed by characteristic x-radiation. The characteristic x-radiation arises from the refilling of the vacancy created in the shell when the electron was captured from it.

Iron-55 (Fe^{55}), formerly used as a tracer for iron, decays by electron capture. There is no gamma radiation associated with Fe^{55}, and the only way that this radioactive decay could be evidenced was by detection of the very soft characteristic x-rays. The use of Fe^{55} has been curtailed in the last few years due to the availability of high specific activity Fe^{59} which is much more easily detectable due to its gamma rays of 1.1 and 1.3 million electron volts.

Chromium-51 (Cr^{51}), commonly used today as an erythrocyte label, decays by electron capture. In about 8% of the cases, this electron capture is followed by a gamma ray of 320 thousand electron volts. Chromium-51 is detected and quantitated by counting the number of 320 Kev. gamma rays given off per unit of time.

Instability.

The instability of a radionuclide is expressed ordinarily in one of three ways, by the decay constant, the half-life, or the specific activity. The first of these, the decay constant, symbolized by λ, expresses the probability that an atom will decay during a particular interval of time. It may also, and is more commonly used to express the fraction of a large number of atoms which will decay during a particular interval of time. The decay constant is then a constant of proportionality, which relates activity expressed in atoms disintegrating per unit time with the number of atoms of the nuclide present. The decay constant is a characteristic of a nuclide. The unit of time ordinarily chosen for expression of activity is the second, since the unit quantity of radioactive isotopes, the curie, is defined in terms of the number of atoms distintegrating per second. λ has the units of reciprocal time, i.e., λ is the fraction of the atoms present decaying per second. $\left(\frac{1}{\text{seconds}} = \text{seconds}^{-1}\right)$

A (atoms distintegrating per second)
λ (fraction of atoms decaying per second)
N (total number of radioactive atoms present)

$$A = \lambda N$$

λ turns out to be a very small number in the case of radionuclides commonly used in clinical medicine and for this reason more convenient units for expression of instability are used.

One such measure of the instability of a radionuclide is the half-life, the time necessary for an original quantity of a radionuclide to decay to one half the original value. Since A, the activity, is related to N, the number of atoms, by a constant, λ, the half-life is also the period of time necessary for the activity of a radionuclide to be reduced to one half the original value. The number of atoms of any radionuclide, N, remaining at time, t, can be found, if the number of atoms, N_0, present at

time, t_0, and the decay constant, λ, are known.

$$N = N_0 e^{-\lambda t} \quad (1)$$

Set N equal to $\frac{1}{2}N_0$, then by definition, the time elapsed from t_0 to t, is the half-life, $T\frac{1}{2}$. Substituting these values in the above equation, and solving for the product of λ and $T\frac{1}{2}$, we find that:

$$\lambda \times T\tfrac{1}{2} = .693 \quad (2)$$

where λ is in time units reciprocal to the time units of half-life.

A more general expression of (1) is:

$$N = N_0 e^{-\frac{.693t}{T\frac{1}{2}}} \quad (3)$$

and since, $A = \lambda N$

$$A = A_0 e^{-\frac{.693t}{T\frac{1}{2}}}$$

Specific activity of a carrier-free radionuclide is an expression of the number of atoms disintegrating per unit of time as a function of the total number of atoms of the radionuclide present. It can easily be shown that specific activity, expressed in this fashion, is equal to the decay constant.

$$\text{Specific Activity} = \frac{\text{A atoms distintegrating per second}}{\text{N atoms present}}$$

But, $A = \lambda N$, therefore:

$$\text{Specific Activity} = \frac{\lambda N}{N} = \lambda$$

This indicates that the higher the decay constant, the higher the specific activity, or, since there is an inverse relationship between λ, and $T\frac{1}{2}$, the longer the half-life the lower the specific activity.

A corollary to this is that one millicurie of a long-lived radionuclide contains more atoms than one millicurie of a radionuclide with short half-life. Therefore, the total number of atoms available for decay is greater, the longer the half-life of a radionuclide. Units of radioactive decay such as the millicurie or microcurie are more often used to indicate the number of atoms disintegrating per unit time, and the unit of mass, the gram or milligram, more often used to indicate the number of atoms present. Specific activity is then stated in millicuries of the radionuclide per gram of the radionuclide for carrier-free radionuclides, and in the case of non-carrier-free radionuclides in terms of millicuries of the radionuclide per gram of the element present.

Specific activity may easily be found in terms of the two variables, half-life, and atomic weight. Let the mass of the radionuclide be 1 gram, then the activity is given by the formula at the bottom of the page.

It is evident that specific activity of carrier-free radionuclides is very high, or stating this another way, the weight of a millicurie is very small. The specific activity of carrier-free I^{131} is 1.2×10^8 millicuries per gram, of carrier-free phosphorus-32 is 2.8×10^8 millicuries per gram. A ten microcurie dose of I^{131} corresponds to administration of only about 80 micro-micrograms of iodine, a ten microcurie dose of P^{32} corresponds to administration of only about 35 micro-micrograms of phosphorus.

The specific activity of carrier-free radionuclides is constant, and is independent of time, since the only atoms of the element present in a source of carrier-free radionuclide are the radioactive ones. The specific activity of non-carrier-free radionuclides varies, depending on the mode of production and chemical treatment necessary for separation after production. Specific activity of nuclides which are not carrier-free vary considerably. The price of a radionuclide is often determined by its specific activity,—the higher the specific activity the higher the price. There are some applications for which lower specific activity radionuclides may be acceptable, in

$$A = \lambda \times N = \frac{.693}{T\frac{1}{2} \text{ in days} \times 86{,}400 \text{ sec/day}} \times \frac{6.02 \times 10^{23} \times 1 \text{ gram}}{\text{atomic weight}}$$

$$= \frac{4.83 \times 10^{18}}{T\frac{1}{2} \text{ days} \times \text{atomic weight}} \text{ disintegrations/second/gram}$$

$$\text{Specific Activity} = \frac{1.3 \times 10^{11}}{T\frac{1}{2} \text{ days} \times \text{atomic weight}} \text{ millicuries/gram}$$

(Avogadro's Number = 6.02×10^{23} atoms per gram atomic weight)

which case considerable savings may be made.

In the case of zinc-65 (Zn^{65}), the price is $2.00 per millicurie for specific activities of 75 to 300 millicuries per gram, while it is $100 per millicurie for specific activities of 5 curies per gram.

The highest specific activity material available is ordinarily used for tracer studies, to minimize chemical effects which introduction of the radionuclide might otherwise produce. The use of iron-59 (Fe^{59}) as a tracer in ferrokinetic studies had to await the development of facilities for production of high specific activity iron-59. Iron-59 available from Oak Ridge has a specific activity of 1,000 millicuries per gram of iron, which is suitable for tracer work when you consider a dose of 20 microcuries of iron-59 would represent introduction of only 20 micrograms of iron, well below the minimum daily requirement for an adult.

Since a non-carrier-free radionuclide is actually a mixture of radioactive and stable isotopes of the same element, the specific activity of this mixture will decrease as time passes, due to decay of the radioactive isotope and constancy of the stable isotope(s).

Modes of Interaction of Ionizing Radiation

Beta radiation.

Beta particles from radionuclides currently used in clinical medicine have maximum energies from about 18,000 electron volts in the case of tritium (H^3), up to about 2.2 million electron volts in the case of yttrium-90 (Y^{90}). Beta particles from a radionuclide do not all have the same energy. There is a distribution of energy from a minimum close to zero, up to a maximum or end point energy which is characteristic of the radionuclide. The most probable, or the average energy of the beta particles from a radionuclide is about one third of the maximum beta particle energy.

Beta particles ionize matter by repelling electrons from atoms as they pass by. About 34 electron volts, on the average, are expended by a beta particle for every ion pair produced. The total number of ions capable of being produced by a beta particle is found by dividing its energy by the energy expended in production of one ion pair. A beta particle of 340,000 electron volts energy would produce about 10,000 ion pairs, according to this.

Due to the small mass of the electron, it has little momentum and is easily deviated from its path. This scattering accounts for the devious path of the beta particle as it passes through matter. In addition, large angle scattering of beta particles by the nuclei of atoms occurs. This backscattering, which is more prevalent with absorbers of high atomic number and beta particles of high energy, results in the production of x-rays, called Bremsstrahlung, or continuous x-radiation. Every source of beta particles is a potential source of x-rays. Due to the inhomogeneity of beta particle energy, and the scattering phenomena, beta particles are absorbed from a beam in a fashion which closely approximates exponential absorption at least for thin absorbers. Since beta particles have finite ranges determined by their energy, there will be some thickness of absorber for any beta emitter which corresponds to the maximum range of beta particles from that source. The maximum range of a beta particle determines the volume of tissue irradiated by beta rays from discrete point sources, the depth of tissue irradiated by beta ray applicators, and the thickness of shielding necessary to protect oneself from beta particles. The maximum range of beta particles varies from about 0.2 mm. water in the case of beta particles from S^{35} or C^{14} up to 27 mm. in the case of beta particles from Cl^{38}.

All that has been said about beta particles applies equally to the positron, except that the positron ionizes by attracting electrons from their orbits, since unlike charged bodies attract each other. Positron emission is always followed by annihilation radiation as previously mentioned.

Interaction of x- and gamma rays.

Gamma and x-rays have very small probabilities for interacting with matter. In the range of x- and gamma ray energies used in clinical medicine, up to about two million electron volts, the probability of interaction is higher in absorbers of high atomic number. The x- or gamma ray photon on interacting with matter may give up all its energy to an electron, producing a secondary electron called a photoelectron whose energy is equal to that of the incident gamma or x-ray, less the energy necessary to remove the electron from the atom. This process is called photoelectric absorption and is an important mode of inter-

action for low energy x- or gamma rays and absorbers of high atomic number.

$$E_\gamma = E_{p.} + \Phi$$

Φ = Binding energy of electron

A photon may interact with matter by transferring part of its energy to an electron, the photon continuing at reduced energy in a direction different from its original path.

$$E_{\gamma_1} = E_{\gamma_2} + E_{C.E.} + \Phi$$

The result is that some of the energy of the primary photon is transferred to the electron, called a compton electron, some is expended in removing the electron from the atom, and some of the energy is retained by the secondary or scattered photon. The angle at which the scattered photon comes off determines the energy imparted to the compton electron. The loss in energy of the photon is often stated in terms of a change in wave length, since the energy of x- or gamma rays is inversely proportional to their wave length.

$$E = \frac{h\ c}{\lambda}$$

E = energy in ergs
h = Planck's constant 6.62×10^{-27} erg sec./cycle
c = velocity of light 3×10^{10} cm./sec.
λ = wave length in cm.

$$\Delta\lambda = .0242\ (1\text{-}\cos\theta)$$

where λ is in Angstrom units (10^{-8} cm.) and θ is the angle formed by the paths of the primary and secondary photon.

This is the principal mode of interaction of x- and gamma rays in tissue in the energy ranges usually encountered in radiation therapy and diagnosis.

Another, less important mode of interaction of electromagnetic radiation is by pair production, which occurs only at x- or gamma ray energies greater than 1.02 Mev. In the vicinity of a heavy nucleus, a gamma ray may be converted to two particles, one an electron, the other a positron, in a process only imperfectly understood which is somewhat the reverse of annihilation of a positron-electron pair. The energy in excess of that necessary to produce the pair, i.e., in excess of 1.02 Mev, is imparted about equally to each member of the pair as kinetic energy. Thus, two secondary ionizing particles are formed in this case. This mode of interaction is important only for very high energy gamma rays in absorbers of high atomic number. We include it in the present discussion only for sake of completeness and will not discuss it further.

The net result of the primary interaction of x- or gamma rays is to produce secondary electrons whose energy varies from slightly above zero to a maximum slightly less than the energy of the incident x- or gamma ray in the case of photoelectric absorption. These secondary electrons produce an effect on tissue by ionizing in the same fashion that beta particles do. This so-called "associated corpuscular emission" is also the agent through which electromagnetic radiation exerts its effect on gases, liquids, and solids in radiation detection instruments.

Units of Measurement

The most common unit of measurement used in tracer work to indicate the quantity of radionuclide present is the microcurie. The microcurie is that quantity of a radionuclide which decays at the rate of 37,000 atoms per second. The millicurie is 1,000 microcuries, and the curie is 1,000 millicuries. Note that the number of atoms decaying per unit time is included in the definition. In order to determine the number and nature of particles and rays given off by any quantity of a radionuclide, we must know something of the decay scheme of the radionuclide. P^{32} gives off only one beta particle per atom disintegrating, therefore, one microcurie of P^{32} would emit 37,000 beta particles per second. Other radionuclides have decay schemes which are more complex.

Nuclide	Beta Particles per Atom Disintegrating	Gamma Rays per Atom Disintegrating
S^{35}	1	0
Na^{24}	1	2
K^{42}	1	.2
Co^{60}	1	2
Fe^{59}	1	1
Cr^{51}	0	.08

Another radiation unit of a different type is the "roentgen." The roentgen is a unit of radiation exposure dose and corresponds to the quantity of x- or gamma radiation which produces through the associated corpuscular emission, ions in air, carrying one electrostatic unit of charge of either sign per 1 cc. of dry air at standard temperature and pressure.

The "rad" is the unit of radiation absorbed dose and corresponds to absorption of 100

ergs per gram of any substance. One roentgen of gamma radiation measured in air, corresponds approximately to one rad absorbed per gram of soft tissue exposed to such a beam, for gamma rays in the clinically useful range.

The gamma ray dose rate constant.

The relationship between the number of millicuries of a radionuclide present and the exposure dose rate from a point source of that nuclide is dependent on the number and energies of gamma rays given off from that source. The relationship is expressed as a dose rate constant, symbolized by the Greek letter Γ.

Γ is the numerical expression of the number of roentgens produced per hour at one centimeter from a point source of one millicurie of the radionuclide.

Nuclide	Γ
Na^{24}	18.4
K^{42}	1.5
Cr^{51}	.18
Fe^{59}	6.1
Co^{60}	12.8
Cu^{64}	1.1
I^{131}	2.18
Cs^{137}	3.2
Au^{198}	2.35
Ra^{226}	8.25

The importance of the unit Γ, lies in its use in radioassay of large quantities of radionuclides by gamma ray dose rate measurements. Γ also enters into dosage calculations for gamma ray emitting radionuclides.

Radiation dosimetry.

Factors which influence radiation dosage where a radionuclide is administered to a patient include, (1) the number and energy of the beta particles or positrons given off per atom disintegrating, (2) the number and energy of gamma rays and their absorption coefficient in tissue, and (3) the half-life of the radionuclide and the biologic half-life of the element. The resultant of radioactive decay and physiologic turnover is to yield an effective half-life for the radionuclide in the body shorter than either the physical half-life of the nuclide or biologic half-time of the element.

$$\frac{1}{T\frac{1}{2}\text{ effective}} = \frac{1}{T\frac{1}{2}\text{ biological}} + \frac{1}{T\frac{1}{2}\text{ physical}}$$

The chemical form of the radionuclide determines the physiologic turnover time, and therefore determines its effective half-life in the body. Tritium has a half-life of 12 years. If the tritium is given as water, the physiologic half-time is only 8 to 12 days, and for this reason, the effective half-life of tritium in the body is only about 8 to 12 days, rather than 12 years. The effective half-life of tritium in some other chemical form, such as a fat or protein, would be different than that for tritium in the form of water. (4) The radiation dose is directly proportional to the concentration of radionuclide per gram of tissue. (5) Size of organ or tissue. Dosage of beta particles is uniform over the major portion of an organ or tissue which is large compared to the range of the beta particles. Dosage falls off toward the surface, within a distance from the surface equal to the range of the beta particles in the tissue. Surface dose is half of what the dose is at a point deeper than the range of the beta particles. Dosage of gamma rays depends on the size of the organ or tissue in addition to concentration. The larger the organ the greater the dose to any point within it as long as the concentration remains constant. The effect of organ size on gamma radiation dose is expressed in terms of a geometrical factor, g, which relates dose to some point in the organ to size and shape of the organ. A point at the center of the organ is chosen to calculate the maximum dose received by the organ.

Beta particle dose for complete decay of a radionuclide uniformly distributed throughout tissue is expressed as:

$$D_b = 73.8\ \bar{E}_b\ T\frac{1}{2}\ C \text{ rads}$$

Gamma ray dose is expressed by:

$$D_\gamma = .0346\ \Gamma\ g\ T\frac{1}{2}\ C \text{ roentgens}$$

Where:
- g is a geometrical factor, which depends on shape and size of tissue.
- Γ is the dose rate constant, roentgens per hour at one centimeter from a point source of one millicurie of the radionuclide.
- $\bar{E}_b$ is the average beta particle energy in Mev.
- $T\frac{1}{2}$ is the effective half-life of the radionuclide in days.
- C is the concentration in microcuries per gram of tissue.

Radiation Detection

The most common types of radiation encountered in diagnostic clinical studies include beta particles, positrons and gamma

rays. In principle, the instruments used for radiation detection are adequate to detect all three types of radiation, but variable sensitivity, design and incidental differences in construction make one instrument more suitable for detection of one type ionizing radiation than another. The choice of detection apparatus depends on the availability of a particular apparatus, the nature and quantity of the radionuclide from which the radiation emanates, and finally, the chemical and/or physical form of the radionuclides.

We will restrict our discussion of radiation detection instruments to the most commonly used types. These are based on the effect of ionizing radiation making air electrically conducting, and the effect of radiation in producing fluorescence in some solutions, plastics, and certain inorganic and organic crystals.

Examples of instruments which operate on the basis of production of ionization in air include the ionization chamber, the proportional counter and the Geiger-Müller counter. All three instruments consist essentially of a gas confining chamber within which are two electrodes, the cathode, or negatively charged electrode, and the anode, or positively charged electrode. The wall of the chamber, at ground potential, often forms the cathode. The anode is several hundred to thousand volts positive with respect to the cathode. The gas contained within the chamber may be air at atmospheric pressure, methane, argon, or mixtures of gases such as helium and isobutane. The ionization chambers are most often used as radiation survey instruments and for calibration of large quantities of gamma emitting radionuclides. When used as rate meters, the intensity of radiation is read directly from a milliammeter mounted on the case. When used as an integrating type instrument the quantity of radiation to which the chamber has been exposed may be read directly from an electroscope which has its scale calibrated in roentgens or milliroentgens rather than in units of voltage or charge. The Lauritsen quartz fibre electroscope is used in our laboratory for calibrating incoming shipments of radionuclides such as I^{131} and Au^{198}. Knowing the dose rate constant for I^{131} and knowing the intensity of radiation at a specified distance from the source, e.g., one meter, it is a simple matter to calculate the quantity of radionuclide present. The pencil type ionization chambers which are worn by radiation workers are examples of integrating type ionization chambers. Some of these ionization chambers are designed to be read on a separate instrument called a minometer, while others have a quartz fibre electroscope included in them to enable the wearer to read the accumulated radiation dose since charging the instrument.

The proportional counter and the Geiger-Müller counter are examples of pulse counting devices which indicate the number of ionizing particles or rays which produce ionization within the chamber. The proportional counter produces a voltage pulse, the magnitude of which is proportional to the energy expended by an ionizing particle in the chamber. The Geiger-Müller counter produces a pulse larger than the proportional counter, but more importantly, the pulses have a magnitude which is independent of the energy expended by the ionizing particle within the chamber. The proportional counter is used to detect the presence of higher energy radiation in the presence of lower energy radiations by choosing pulses whose magnitude is above a certain level chosen by the operator: e.g., in a mixture of Sr^{90} and Y^{90}, a radioactive parent-daughter pair, it is possible to count the 2.2 Mev beta particles from yttrium-90 in the presence of the .54 Mev beta particles from strontium-90 by choosing only pulses caused by beta particles greater than .54 Mev. This is done by means of an instrument called a pulse height discriminator, or selector.

Geiger-Müller counters operate on an "all-or-none" principle, and if a particle has sufficient energy to enter the chamber and produce even one ion pair, it is possible for it to be counted.

It is possible, then, with pulse counters to detect the presence of as little as one atom, since every time a beta particle enters the chamber and is counted, it represents the decay of one atom of a radionuclide. The sensitivity of Geiger-Müller and proportional counters is dependent on the design of the tube or chamber. There are available proportional and Geiger-Müller counters which permit introduction of a sample directly into the chamber. This type instrument, called a "flow-type" proportional or Geiger-Müller counter, requires a constant supply of gas from a tank

to replenish losses from leakage. It is possible with flow-type instruments to detect close to 100% of all the beta particles given off by a source of radiation within them.

Proportional counters do not find widespread use as survey type instruments due to stringent requirements on voltage regulation. Geiger-Müller counters on the other hand have need for minimal voltage regulations, can be operated easily from dry cell batteries, and find widespread use as survey type instruments. Proportional and Geiger-Müller counters are used principally to indicate the number of beta particles or other ionizing radiation detected per unit time, and do not measure dose rate in terms of roentgens as the ionization chamber does.

The fluorescent effect of ionizing radiation is taken advantage of in another type radiation detection instrument. Scintillation counting as this method is called, first found use in detection of alpha particles with zinc sulfide screens, such as the Spinthariscope used by Rutherford and other early workers. Later, due to the high gamma ray detection efficiency of crystals such as thallium activated sodium iodide, and calcium tungstate, the method was extended to gamma ray detection. More recently, liquids, gels, and plastics have been used for detection of beta particles with excellent results. Tritium, carbon-14 and sulfur-35, so difficult to count with gas ionization type instruments due to low sensitivity due to self-absorption in solid or liquid sources, can now be counted with detection efficiency of the order of 10 to 50% in liquid scintillation counters.

The low inherent efficiency of Geiger-Müller type instruments for detection of gamma radiation demanded development of more efficient detection methods. One of the first effects of ionizing radiation noted by Roentgen and other early workers was the fluorescent effect which radiation had on certain crystals. Zinc sulfide thinly coated on a glass plate formed one of the first radiation detection instruments. The scintillations were counted visually to estimate the activity of a sample. Since the human eye is rather limited in its ability to detect two independent events at short intervals of time, counting by this method fell into disuse with the advent of the Geiger-Müller counter, which could operate at very high counting rates. However, with the development of the photomultiplier tube, it became possible to count the number of scintillations occurring in a crystal, by imparting the energy of the photons of light from the crystal, to electrons in the photomultiplier tube. The number of electrons can be amplified or multiplied in the photomultiplier tube, resulting ultimately in a pulse from the photomultiplier tube which is capable of being counted by an electronic counting device such as a scaler and/or mechanical register.

Scintillating fluors are available in a wide variety of sizes, shapes, and materials. The most commonly used fluor for gamma ray counting is thallium activated sodium iodide. Crystals are commercially available for routine clinical use in sizes up to 3 x 3 inch right cylinders, and even larger sizes for special purposes, such as total body counting where crystals as large as 8 inches diameter by 4 inches thickness are not uncommon.

Scintillation counters are used as movable probes to detect the presence of radiation *in vivo*, or as well type detectors into which samples of radioactive materials may be inserted.

The scintillation counter behaves very much like a proportional counter in that the pulses produced by it are proportional in amplitude to the energy expended by gamma rays in the crystal. This, coupled with the ability to selectively count pulses of desired amplitude with a pulse height analyzer, makes the scintillation counter a very powerful tool for identification of radionuclides. It is almost a necessity to use a scintillation counter with a pulse height analyzer to get accurate results in *in vivo* counting. The pulse height analyzer enables one to detect the primary gamma radiation from the source being counted in the presence of radiation scattered from the source and surroundings. Efficiency of detection of ionizing radiation from e.g., I^{131} in a well type counter is about 35 to 40%, that is, 35 to 40 counts for each 100 atoms of I^{131} which decay.

Detection of Radiation in Practice

The quantity of radioactive material necessary for performance of a diagnostic study is dependent on several factors, included among which are the inherent sensitivity of the detection device, the background radiation to which the detector is exposed, the size and

physical form of the sample counted and, finally, the time duration of the counting operation. Geiger-Müller counters have a detection efficiency of about 100% for any beta particles which enter the sensitive volume of the chamber. The detection efficiency of a Geiger-Müller tube is about 1% for gamma rays traversing the sensitive volume. It is apparent that for detection of gamma radiation more sensitive detectors than Geiger-Müller tubes should be used to minimize the dose of radioactive material necessary to perform a diagnostic study.

The highest detection efficiency is found where the detector completely surrounds the source of radiation. This type configuration is called 4 pi geometry. Where the detector subtends a solid angle from the source equal to a hemisphere we have 2 pi geometry, and can theoretically detect 50% of the rays of particles emanating from the source. The greater the distance between source and detector the less the detection efficiency, since the detector subtends a smaller solid angle from the source and intercepts a smaller number of rays or particles. By placing sources of beta radiation such as P^{32} in front of Geiger-Müller tubes with thin walls, it is possible to detect 20% of the beta particles given off from such a source. Weaker beta emitters, such as H^3, C^{14}, or S^{35}, are often counted in flow-type counters with 2 or 4 pi geometry, or in liquid scintillation counters to achieve detection efficiencies of this order of magnitude.

There are many technical difficulties involved in sample preparation and counting of beta emitters. Therefore, gamma rays, if present, are most often detected and counted due to lack of restriction on source size and configuration. Fe^{59}, Co^{60}, Cu^{64}, As^{74}, I^{131}, and Au^{198}, all yield gamma as well as beta radiation. Rarely are any of these quantitated by beta counting. Since they all emit gamma rays of conveniently detectable energies, these sources are most often assayed by gamma counting. Due to its high atomic number, high density, and inherent sensitivity, the sodium iodide scintillation counter is the instrument of choice for gamma ray detection in the case of these nuclides.

Crystals of dimensions of the order of 2 to 3 inches diameter by 2 to 3 inches height are commonly used today. These crystals may be machined in the form of a well such that test tubes or other containers holding solutions of radioactive materials may be placed within them. The source of radiation is then almost completely surrounded by the radiation detector. As mentioned previously, I^{131} may be detected in this type instrument with 35 to 40% efficiency. Due to the few number of gamma rays given off by Cr^{51} (8 gamma rays per 100 disintegrations), the efficiency is somewhat lower (5%) for detection of Cr^{51}.

The sensitivity of a scintillation counter for detection of radiation from a source at some distance from it is a direct function of the cross sectional area of the crystal. Sensitivity increases with thickness also, but not linearly since the beam of radiation is attenuated as it passes deeper into the crystal. Although the sensitivity of a scintillation counter increases with size, the background also increases. Radioactive materials in the environment such as radium and its daughter products, potassium-40, cosmic radiation, fallout, and local sources of ionizing radiation all contribute to background radiation. Background may be minimized by shielding the detector with several inches of lead or iron, but there is a diminishing return on reduction of background radiation in this fashion. Well type detectors frequently have from 2 to 4 inches of lead shielding around them, while probe type detectors, due to the need for mobility and flexibility in positioning, have from one to three inches of lead surrounding them.

The background radiation determines the minimum quantity of radionuclide detectable, since in order to be detected in the presence of background, a sample must have a gross counting rate greater than the upper limit of the range of background. In a practical situation the dose necessary for a diagnostic study is based on achieving sufficient activity in the assay sample to exceed the background counting rate by a factor of about 5 to 10 to minimize errors due to variation in background.

The longer a sample is counted the greater the accuracy in the result obtained, since errors due to the randomness of radioactive decay are minimized. Due to economy of time, 5 minutes is about the maximum time allotted to counting samples for blood and plasma volume determinations or for counting patients for thyroid uptake studies. Errors in timing obviate the use of counting times much shorter than one minute.

The product of counting rate and time is merely total counts, and in any event the accuracy of results obtained is limited by the number of counts accumulated while counting a source. The randomness associated with radioactive decay is such that a series of counts taken with a radiation detector will not be repeated exactly, but will fall around some average, just as the heights or weights of people if plotted as a frequency distribution would fall about some average value. The spread or variability in weight or height of individuals is expressed by an experimentally derived figure, the standard deviation. The standard deviation of a group of replicate counts on a sample of radioactive material, which does not decay appreciably during the time of observation, is always equal theoretically to the positive square root of the average number of counts. If we had a long series of counts whose average was 100 counts per observation period, the standard deviation would be the root of 100, or 10 counts. The relative standard deviation is then the standard deviation expressed as a per cent of the average number of counts, and in this case would be 10 per cent. For samples taken from the same population, but counted for a longer period of time, in which the average number of counts per observation was, say, 900 counts, the relative standard deviation would be only 3.3 per cent. This indicates less variability in results with increased counting time.

Variability in the preparation of the sample is not nearly as important in gamma ray counting as it is in beta particle counting, since the effects of self-absorption in the source of radiation or its container are minimal with gamma radiation. Relative gamma ray counting by comparison under identical geometrical conditions with standards prepared in the same fashion as the sample obviate any corrections for source size, shape, position or configuration.

In vivo counting of gamma emitters is not so simple. Although Geiger-Müller counters have been and still are used for performing thyroid uptake studies, the most practical and sensitive means of *in vivo* detection, localization and assay of gamma emitting radionuclides is by means of the NaI crystal scintillation counter.

To reduce background radiation, the scintillation probe is surrounded with a cylindrical lead sleeve of from one to three inches thickness. This sleeve extends from several inches behind the crystal to several inches in front of it, forming a shield which reduces the intensity of radiation from all points other than that from which desired. Variations in thickness, length, diameter, shape, etc., can be found depending on the purpose of the probe. The "honey cone," multiple aperture, focusing collimator is one such variation on the basic collimator.

If we take as an example, the problem of determining the quantity of I^{131} in the thyroid gland, we see that the instrument should be so shielded that it efficiently detects radiation coming from the thyroid gland but not from the rest of the body. The purpose of the collimator is to do this. However, lead, or any absorbing material for that matter, is not completely impervious to gamma radiation and some gamma radiation, particularly the higher energy gamma rays will come through the walls of the lead collimator.

Some of the gamma radiation coming from the thyroid gland will be absorbed in the gland and overlying tissue, reducing the apparent I^{131} activity as determined by the detector. Some gamma radiation will initially start out in a direction other than toward the detector, interact with other tissues of the patient's own body or surroundings, be reduced in energy and scatter back into the detector, raising the apparent activity in the thyroid gland detected by the probe.

There is a twofold approach to the solution of this problem. One is to place a "standard" source of I^{131} in a container which is designed to absorb and scatter the gamma radiation in the same way as the patient did. In this way, the apparent variation in thyroid activity due to scatter and absorption is partially corrected. The thyroid uptake is found by comparing the apparent activity in the thyroid gland with the apparent activity from a "standard" source equal in quantity or proportional to the dose administered to the patient.

The second approach, more applicable to all types of *in vivo* counting, is to use a detection system preferentially sensitive to gamma rays within a narrow energy range. Such an instrument is a pulse height analyzer. The previous problem of minimizing effects due to

gamma ray scattering may be solved with such an instrument. In addition, the effects of background and higher energy gamma rays which penetrate the lead collimator are minimized.

In the case of I^{131} detection, the preferential sensitivity of the pulse height analyzer is so adjusted that pulses from the scintillation counter corresponding to photoelectric absorption of the 364 Kev. gamma rays are passed to the scaler for counting. All other scattered or primary gamma rays above or below the limits chosen are rejected and not counted.

The ability to perform multiple diagnostic studies with two or more gamma ray emitters lies in the variable preferential sensitivity of this type instrument. Simultaneous studies of red blood cell utilization of Fe^{59} and survival of Cr^{51} labeled erythrocytes are conveniently performed with the aid of the pulse height analyzer.

Radiation Protection

The simplest methods of protection against ionizing radiations are the same ones which people have learned to use long ago to protect themselves from overexposure to the rays from the sun, or heat from a fire. The first and simplest is to minimize the time of exposure, since the cumulative radiation dose is the product of time and exposure dose rate. This may well be the most economical method of radiation protection. The second method is to place as much distance between the individual and the source as is practical. At distances close to the source, small changes in distance produce large changes in radiation intensity, since for point sources of electromagnetic radiation, the intensity varies inversely as the square of the distance from the source. There is a limit in the practical situation to how little time one can spend in the vicinity of a source of radiation, and how much distance one can put between oneself and the source of radiation.

Shielding is the third method of reduction of radiation exposure. Beta particles are conveniently shielded by thin layers of material of low atomic number to minimize Bremsstrahlung. One centimeter of unit density plastic is sufficient to absorb all the beta particles from a source of P^{32}. Any absorber would do for gamma rays, but to get the greatest shielding effect with the most efficient utilization of space, high density materials such as lead, iron, or concrete are used in the laboratory. Water is perfectly acceptable as a gamma ray shield but larger thicknesses of it are required to produce the same reduction in intensity as for a given slab of iron or lead. Gamma radiation is absorbed exponentially, and is theoretically never completely attenuated. The reduction of a beam of gamma rays from cobalt-60 as a function of shielding thickness is given in table 1.

TABLE 1

Intensity of Radiation	*Thickness of Lead Shield*
100 mr/hr.	0 cm.
50 mr/hr.	1.2 cm.
25 mr/hr.	2.4 cm.
12.5 mr/hr.	3.6 cm.

From this table we see that the half thickness of lead for attenuation of gamma rays from cobalt-60 is 1.2 cm. Successive layers of 1.2 cm. each would reduce the radiation by one half for each layer added.

Summary

A necessarily brief, simplified presentation of some of the physical principles underlying the clinical use of radioactive isotopes of the elements has been given. The material presented is far from complete and many important considerations have been omitted purposely for the sake of brevity. Approximations have been used wherever possible to facilitate understanding, and many facts treated in a qualitative manner, rather than by rigorous presentation.

A few general reference works are:

1. Radioisotopes in Clinical Practice. Part I and II. Quimby, Feitelberg and Silver. Philadelphia, Lea & Febiger, 1958.
2. Clinical Use of Radioisotopes, Ch. 1. Beierwaltes, Johnson and Solari. Philadelphia, W. B. Saunders Company, 1957.
3. Atomic Medicine, 3rd Ed., Ch. 1, 2, 5, 6, 15, and 22. Edited by RADM C. F. Behrens, USN (Ret.). Baltimore, Williams & Wilkins Company, 1959.

Important Applications of Nuclear Medicine in Pathology*

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Introduction

THE USE OF RADIOACTIVE ISOTOPES in the pathologic laboratory has been slow in developing. This is partly explained on the basis of the restrictions on the use of these new tools, and partly on the difficulty of obtaining training in their use. However, at the present time many radioactive elements are available in almost every community in the country through the pathologist of the community. These tests, although simple, safe and accurate, are nevertheless too poorly understood by the average physician to be a part of the diagnostic facilities which he is able to use. It is to be hoped that in the coming years the information on these substances will become more widely distributed to physicians. Furthermore, it is hoped that symposia such as this one sponsored by the Southern Medical Association will help to distribute the information on how these substances may be used to facilitate diagnosis and treatment of disease. We will discuss at this time the commonly used radioactive isotope technics, those which are readily available, highly accurate and which are beyond the stage of research.

Tests of Thyroid Function

Preparation for the Radioactive Uptake Test. Patients should be scheduled for the test and come into the laboratory after fasting one to two hours to assure an empty stomach.

Because the test is new and many physicians are not aware of its limitations, a brief history is taken to avoid unsatisfactory result with consequent undue expense to the patient and loss of trust in the test by the physician. The following substances interfere with thyroid function and, consequently, with its handling of the radioactive iodine.

1. Thyroid hormone, cortisone, ACTH, testosterone and estrogen all suppress thyroid function to some degree.

2. Thiocyanate blocks uptake of iodine.

3. Iodine medication, such as in certain cough mixtures and preparations for asthmatics, saturates the gland and interferes with the uptake.

4. X-ray diagnostic procedures using iodized radiopaque dyes, such as for the gallbladder, intravenous pyelogram, bronchogram and myelogram, also act as saturating agents.

5. Propylthiouracil, other similar compounds, and medication with sulfonamides cause the gland to show an increased uptake of iodine. Although they block the organic binding of iodine in the gland, they usually cause an increased avidity of the gland for iodine.

Patients should be off inorganic iodine and hormonal therapy for about one month. Radiopaque dyes act as blockers for 6 months, or a year in some cases. Propylthiouracil and thiocyanate should be discontinued from 6 to 8 weeks before the uptake is measured.

Procedure. After the history is obtained the patient is given a standard dose of I^{131}. The patient is told to fast for about one hour until the iodine is absorbed. Although small amounts of iodized salt do not interfere with the test, we usually advise patients to avoid extra salt, seafood, and cabbage during the following 24 hours. The patient is then told to return in 24 hours.

When the patient returns his neck is palpated to find the thyroid. The scintillation probe is then adjusted to count for 3 minutes at the measured distance from a point just above the isthmus of the gland.

The patient's corrected counts per minute are divided by the standard corrected counts per minute (which is equal to 100% of the dose) to obtain the per cent uptake by the gland.

The sternal area may be checked for sub-

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sternal goiter, and lateral nodules in the neck may be checked for activity. However, metastatic thyroid tissue rarely picks up enough iodine when the thyroid gland is still present to compete with it.

After measuring uptake, a 10 to 15 ml. sample of blood is withdrawn, and a 3 ml. sample of liquid saliva is obtained.

The whole serum is counted for activity. Then a protein extraction is made, and the amount of activity in the protein fraction of the serum is obtained.

A sample of saliva of equal volume to that of the serum is then counted. We thus obtain:

$$\frac{\text{Protein-bound } I^{131}}{\text{Whole serum } I^{131}} = \text{x 100 per cent (conversion ratio)}$$

$$\frac{\text{Saliva } I^{131}}{\text{Protein-bound } I^{131}} = \text{saliva ratio}$$

An additional determination which we do not do as a routine is the urinary excretion of iodine. This is done simply by measuring an aliquot of a 24 hour specimen to determine the total amount of activity excreted in 24 hours. This value is compared with the total activity of the standard which is determined by measuring an aliquot of the standard in the well counter. The per cent of the dose administered that is excreted is thus obtained.

Interpretation. Per cent uptake is obviously a measure of the avidity of the gland for iodine and is, of course, elevated in a gland that is hyperfunctioning.

Conversion ratio is likewise obvious since the actively functioning gland turns inorganic iodine over rapidly into protein-bound iodine.

The salivary iodine was first discovered as a measure of thyroid function by Thode, Jaimet and Kirkwood.[1] They explained that the test was dependent on an enzyme, tyrosine iodinase, present in the salivary glands. They postulated some inverse functional arrangement between thyroid function and salivary gland function. This theory was later refuted by Freinkel and Ingbar[2] who showed that the ratio was really dependent on the ratio of circulating protein-bound I^{131} to inorganic I^{131}. If most of the I^{131} is protein-bound, as would occur in hyperthyroidism, then little would be secreted by the salivary glands, since that which they secrete has been proven to be the inorganic form. Consequently, the ratio of salivary activity to plasma protein-bound activity would be low. However, if the PBI^{131} were low, as would occur in hypothyroidism, the salivary glands would have more inorganic I^{131} to secrete and the latter would be high. So the test really measures in an indirect manner the amount of I^{131} not picked up or converted to PBI^{131} by the thyroid gland.

The urinary I^{131} measures, of course, that iodine not retained by the system. It is sometimes used in cases of cancer of the thyroid where presumably all the tumor has been eradicated. If large amounts of I^{131} are still retained, presumably there is occult functioning tumor tissue in the body and therapeutic I^{131} should be given. Actually this test is not too accurate since up to 10% of a tracer dose may remain unaccounted for even in the normal individual.

There is some overlapping between values when it comes to actually interpreting the results obtained. I have used the following chart in which the values obtained are compared with the other tests of thyroid function.

THYROID PROFILE CHART[20]

	% I^{131} Uptake	% PB I^{131}	Saliva I^{131}	Chem. PBI	BMR	Cholesterol
Hyperthyroid	50	50	40	8.0	+15	150—
Euthyroid	40	40	160	7.8	+10	175
	15	15	235	4.0	—10	
Hyperthyroid	50	50	40	8.0	+15	250+

It will be noted that there are wide zones on each side of euthyroidism where values are borderline and must be interpreted along with clinical manifestations, as are all laboratory tests. There perhaps should also be some overlapping into the euthyroid zone, but this is more ill-defined. I have found the salivary iodine to be of value only in interpreting cases of hypothyroidism. High values above a ratio of 338 are much in favor of hypothyroidism, whereas values in the lower ranges occur in euthyroidism as well as in hyperthyroidism.

T-3 Test. In addition to the previously mentioned tests, tri-iodo-thyronine tagged with I^{131} may be utilized in the diagnosis of thyroid disease. A fresh sample of blood is drawn and an aliquot of the blood is mixed with a small amount of tri-iodo-thyronine tagged with I^{131}. The red cells of the patient will pick up tri-iodo-thyronine in quantities between 10 and 18% of the dose. The red cells are counted following exposure and washing to determine the amount of tri-iodo-

thyronine that has been taken up by the red cells. This measures the amount of thyroid activity. If below 10% the patient is considered to be hypothyroid, and above 18% the patient is considered to be hyperthyroid. This test may be used under any circumstances and is not interfered with by drugs containing iodine or other agents which block the I^{131} in the uptake test.

Circulatory Studies with Isotopes

Circulation time can be determined satisfactorily by the use of RISA (Radio-iodinated Serum Albumin).

The circulation time may be determined by placing a scintillation detector over the precordium and another over the hand. A 100 μc dose of RISA is then injected and its time of appearance at the two sites is timed. Some investigators have hooked the precordial detector to an Esterline-Angus rate meter and cannulated an artery so as to run blood through a helix arrangement in a plastic tube around another detector. With this set-up they can determine cardiac output.

Cobalt-60—Vitamin B_{12}. Because of the widespread use of preparations containing B_{12} and intrinsic factor by practitioners, it has become increasingly difficult to make a positive diagnosis of pernicious anemia without allowing the patient to have a relapse. It has also become very difficult to obtain cases suitable for assay of intrinsic factors. What has been needed is a test that may be used in a treated patient and which can tell us the response to intrinsic factor.

Since B_{12} tagged with Co^{60} has become available, three tests have been designed to measure the patient's ability to absorb B_{12} and, consequently, his possession or lack of the intrinsic factor.

First, Heinle, Welch and associates[3] determined the fecal excretion of Co^{60}-B_{12} in patients with pernicious anemia following a standard test dose of 0.5 μg Co^{60}-B_{12} with and without added intrinsic factor.

Second was a test by Schilling.[4] An oral dose of 2 μg Co^{60}-B_{12} is followed by a flushing dose of 1,000 μg of nonradioactive B_{12} given intramuscularly. The principle is that the patient who absorbs more of the oral Co^{60}-B_{12} will excrete more in the urine when the large flushing dose is given. If little or none is absorbed the urine will contain very little.

The third test, described by Glass, Boyd, and associates,[5] is based upon determination of the uptake of radioactivity by the liver when a potent preparation of intrinsic factor is given orally to a patient with pernicious anemia together with a standard dose of 0.5 to 2 μg of radioactive Co^{60}-B_{12}.

Equivocal results have been obtained in sprue, but the lack of response of the patient to intrinsic factor preparations and the good response to folic acid should aid in the diagnosis.

It has been definitely determined that the Co^{60} substance measured in the urine in the Schilling test is actually still $B_{12\ 17}$.

The combination of radioactive Co^{60}-B_{12} with nonradioactive B_{12} must be carefully adjusted to obtain proper results, since there is evidence that the efficiency of intestinal absorption decreases with increased uptake. There may be an intestinal B_{12} acceptor similar to apoferritin for iron. When this becomes saturated no absorption takes place. Glass, Boyd and associates have considered calling it B_{12} transferrin.

Iron-59. Radioactive iron can be used to study the metabolism of iron in the body, i.e., its absorption and distribution. Also, because of its incorporation into the hemoglobin complex, it is a valuable tool in studying the manufacture of red blood cells.

Moore, Dubach, and associates[6] studied the intestinal absorption of ferrous and ferric iron by normal and anemic subjects with radioactive iron. They found that all subjects absorbed ferrous iron more readily than ferric (ratio 1½ to 15 times greater for ferrous iron).

The same groups, in 1955, reported on the distribution of iron in humans and showed that the calculated iron excretion in the feces in normal subjects was 0.33 to 0.52 mg. per day.[7] For iron-deficient patients it was 0.3 to 0.06 mg. per day. For a woman with hemolytic anemia it was 1.45 mg. per day and for a man, 0.3 mg. per day.

Many studies have been done on the turnover of iron in hemochromatosis. Bothwell and associates[8] investigated 4 cases of hemochromatosis and 11 normal people. They found that the mean plasma iron turnover

was significantly raised in hemochromatosis while the red blood cell turnover was normal. The percentage of the dose of radioiron used for hemoglobin formation was less in hemochromatosis. Repeated phlebotomies were well tolerated and caused a marked and sustained plasma iron turnover. The red blood cell-iron turnover also appeared to be increased and the percentage of the dose utilized was raised, although it was still lower than normal.

Several studies have been done on the plasma clearance and red blood cell utilization of Fe^{59}. Since about 21 mg. of iron is the daily requirement for hemoglobin production, and since that circulating in the plasma is only about 3 mg., iron must enter the plasma from the spleen and other reticuloendothelial tissues at the same rate at which it leaves to be incorporated into red blood cells.

The rate of iron clearance from the plasma must, therefore, represent a composite of all pathways involved and a reflection of the functional status of hematopoiesis. Exceptions are the cases of pernicious anemia and Mediterranean anemia in which iron is stored but not used. A more direct and accurate index of hematopoietic activity is the rate of incorporation of iron in the new-formed red blood cells.

To determine the plasma clearance, one injects tagged plasma containing 20 μc of Fe^{59} citrate and obtains samples of blood at 5, 15, 30, 60 and 120 minutes after injection. The plasma activity is determined and the values plotted on semilog paper against time. By extrapolating to zero time with the curve, the disappearance or turnover half-time is determined. Blood samples are obtained at 3, 7 and 14 days to determine the incorporation of Fe^{59} into the red blood cells.

Normally the plasma half-time is from 1 to 2 hours. In iron deficiency, hemolytic disorders and polycythemia in which there is a rapid turnover of Fe^{59}, it is only 0.3 to 0.5 hours. In aplastic anemia it is 2 to 4 hours. The exceptions are pernicious anemia and Mediterranean anemia, in which the turnover is also rapid, 0.3 to 0.5 hours. However, the rate of incorporation into the red blood cells tells a more accurate story of hematopoiesis. If there is about a 90% uptake by the red blood cells in one week in normal subjects, there is a value approaching 100% in 3 to 4 days in iron deficiency cases. In aplastic anemias, pernicious anemia, and Mediterranean anemia there is a slow rise over many weeks as the iron is slowly incorporated.

Chromium-51. Cr^{51}, when incubated with the red blood cells of a patient, enters the cells and is transformed into a nondiffusible form providing a reasonably permanent label. The amount used would not constitute a hazard chemically because of the high specific activity of chromium.

Red blood cells tagged with chromium can be used to measure blood volume of the patient or the red blood cell survival time of a particular patient's red blood cells. As will be discussed in the simple isotope dilution principle used in estimating blood volume with RISA, a similar type of procedure can be used employing the same isotope dilution principle to measure the red blood cell mass directly. After finding the red blood cell mass and knowing the hematocrit, the total blood volume and plasma volume can be determined from these figures.

In determining the red blood cell survival, a dose of 100 μc is administered directly into the circulation, or the blood may be withdrawn and tagged. Counts are made in 24 hours (zero time) and taken as 100% survivals. This allows time for the unbound chromium to be eluted from the circulation by way of the kidneys and, therefore, will not interfere with the determinations by contaminating the red blood cell mass with plasma-containing unbound chromium. Further counts are then taken at 2 to 3 day intervals for 4 to 6 weeks. Counts are taken to determine the half-time survival of the red blood cells with a 24 hour sample being considered as equal to 100% survival.

Weinstein and Beutler[9] used Cr^{51} and Fe^{59} in a combined procedure to study erythrocyte production and destruction in the normal human patient and in patients with hemolytic or aplastic anemia. The markedly shortened survival time in hemolytic anemia with normal survival times in other conditions was noted. The more rapid iron utilization in hemolytic anemia and the poor utilization in the aplastic anemia were also observed.

I^{131} for Testing Protein and Fat Digestion

Iodine-131 blood levels were measured in normal patients following ingestion of a radio-

active labeled protein (RISA) test meal.[11] The gastric emptying time was determined simultaneously. A set of similar determinations were carried out in another group of normal subjects[12] following the ingestion of a fat meal tagged with I^{131} (I^{131} labeled glycerol trioleate). It was found that as the meals were digested the iodine-131 was freed and entered the blood stream. A characteristic and reproducible curve of radioisotope blood levels was obtained in each case. Radiographic determination of gastric emptying was found necessary for interpretation of the data. The implications are, of course, that this might be standardized as a clinical procedure, if necessary.

RISA for Blood Volume Determination

Human albumin has been tagged with I^{131} and the preparation called Radio-iodinated Serum Albumin (Human). The physical and chemical properties of the albumin remain unchanged, and therefore it constitutes an ideal mixer in the plasma. The procedure is then based on the isotope dilution principle which is so commonly used in most isotope procedures.

RISA is made up to a concentration of 3 to 5 μc per ml. in a stock bottle before use. A 1 ml. sample is withdrawn from the stock bottle and injected into the 1,000 ml. volume flask. Exactly the same amount is again drawn into the same needle and syringe from the same stock bottle and injected into the patient's vein. After waiting 10 to 15 minutes for mixing to occur, a sample of blood is withdrawn from the opposite arm without stasis and put into a heparinized or oxalated tube. A sample of this is used for hematocrit determination. The remainder of the sample is spun down in a centrifuge and two 3 ml. samples of plasma are withdrawn and counted for radioactivity.

This simple procedure may be repeated quite often (10 to 20 times) in a patient, since very little active substance is injected. This has an advantage over the Evans' Blue method. In repeating the procedure a sample of blood must be obtained before injecting the RISA to determine residual or background activity of the patient's plasma. There is a practical accuracy of 95 to 97% in the method.

The information obtained may be important in the management of fluid balance in major surgical procedures and burn cases. It will also be of value as an aid in diagnosing polycythemia vera, since there should be a rise in the total red blood cell mass in this condition. It is also of value in cases of cardiac decompensation, since it has been shown that the total blood volume is increased when the heart is decompensated. Surgeons doing heart surgery find it a very valuable guide as to when they may operate.

Other determinations, such as hemoglobin and serum proteins, used in conjunction with this test give a 3-dimensional picture.

Summary

This paper has discussed the diagnosis of thyroid function by the use of radioactive iodine and the different function tests which are largely related to the uptake of iodine in the thyroid gland. The newer test, the T-3 test, measuring the uptake of tri-iodo-thyronine in the red cells, offers great promise.

Circulatory studies testing the speed of circulation with I^{131} is very helpful in vascular and cardiac diseases.

The diagnosis of pernicious anemia is greatly facilitated by radioactive cobalt incorporated in B_{12}.

Iron-59 enables one to identify the iron stores in the body and to follow the metabolism of red cells and hemoglobin through the body. Iron absorption studies of the gastrointestinal tract are also very helpful.

Chromium-51 may be used for blood volume studies as well as red cell survival studies in hemolytic disease.

Fats and proteins tagged with I^{131} may be used for measurement of the gastrointestinal digestive ability.

Albumin tagged with radioactive I^{131} may be used similar to chromium in the testing of blood volume.

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The Internist's Viewpoint on the Use of Radioactive Iodine in Thyroid Disorders and Cardiac Abnormalities

I. Diagnostic Procedures for the Estimation of Thyroid Function*

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WITH THE ADVENT of the nuclear age and the abundant availability of radioisotopes, a new group of clinical laboratory tests have taken their place among those useful for estimating thyroid function. These are tests in which radioiodine, I^{131}, is utilized.

Iodine Metabolism and Thyroid Physiology

An understanding of iodine metabolism and thyroid physiology is essential to the evaluation of thyroid function by means of diagnostic tests with radioiodine.

Most iodine enters the body by ingestion and is rapidly absorbed in the upper gastrointestinal tract. Some absorption can occur through the skin and through the mucous membranes of the respiratory and genital tracts. Iodine is transported through the plasma as iodide ions, which are then removed from the circulation either by being trapped in the thyroid gland or by being excreted through the kidneys. The plasma iodide taken up by the thyroid is transformed to iodine and is introduced into the tyrosin molecule to form diiodotyrosine (T2). Two molecules of this latter compound are then joined to form thyroxin (T4), which may be further transformed to thyroglobulin and stored in the colloid of the gland. Some of the thyroxin is secreted directly into the blood stream. Commensurate with the metabolic needs of the individual, there is proteolysis of the thyroglobulin and it is released into the circulation as thyroxin. Some investigators believe that further reduction of thyroxin (T4) to tri-iodothyronine (T3) is necessary for the thyroid hormone to be active at the cellular level. This aspect of thyroid physiology is controversial.

The activity of the thyroid gland, including the initial uptake of iodide ions is regulated by the thyroid-stimulating hormone of the pituitary (TSH.). The secretion of TSH. by the pituitary is, in turn, dependent upon the level of thyroid hormone in the circulation. Circulatory thyroid hormone also has a direct inhibitory effect upon the activity of the thyroid gland. T3 has similar inhibiting effects.

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There are also other inhibiting substances. Although the mechanism has never been clearly understood, it is a well-known fact that saturation of the thyroid with iodine inhibits further uptake and subsequent organic binding of iodide. Drugs of the thiourea group prevent the synthesis of thyroid hormone by blocking the organic binding of iodine to tyrosine.

Diagnostic Tests With I^{131}

The clinical procedures outlined below can give information about the uptake of I^{131} by the thyroid and about the synthesis and secretion of thyroid hormone by the gland.

A. *Radioiodine Uptake Tests*
   1. Rate of thyroidal uptake.
   2. Percentage of thyroidal uptake.
      24 hour uptake
      6 hour uptake
   3. Rate and percentage of urinary excretion.

B. *Radioiodine Secretion Tests*
   1. Protein bound I^{131} (PBI^{131}).
   2. Conversion ratio (PBI^{131}: Total Plasma I^{131}).

Neither of these groups of tests directly measure thyroid function or the end metabolic effect of thyroid hormone. Unfortunately, the clinician continues to have only presumptive tests of thyroid function to aid him in the differential diagnosis of clinical thyroid disorders. The thyroidal uptake of radioiodine measures the avidity of the gland for iodine. Since iodine is the principal building block in thyroid hormone synthesis, it is assumed that the gland takes up this element for this purpose and in quantities proportional to its production rate. It is further assumed that a state of equilibrium exists between the rate of uptake of iodine and the rate of secretion of thyroxin by the thyroid. Thus, percentage uptakes of radioiodine that are lower or higher than established normals are presumptive evidence of decreased or increased thyroid function. The measurement of the percentage of thyroidal uptake of I^{131} is the simplest and most commonly used test. The most widely employed radioiodine secretion test is the determination of the PBI^{131} conversion ratio. The remainder of this presentation will for the most part be devoted to the discussion of these two tests.

Thyroidal Uptake of I^{131}

Rate of Thyroidal Uptake. The true measurement of the rate of uptake of I^{131} by the thyroid requires the determination of the clearance rate. This, however, is a somewhat difficult and time consuming procedure. It can be determined indirectly by determination of the accumulation gradient from percentage uptakes of a tracer dose present in the gland at various times after administration. Any correlation of the clearance rate to the accumulation gradient must, of course, be based on the supposition that there is no discharge of I^{131} from the gland during the time span of the measurements. In some hyperthyroid patients the metabolic turnover of I^{131} is so rapid that appreciable discharge of the iodine incorporated into thyroid hormone takes place after 6 to 10 hours.

Percentage of Thyroidal Uptake. As was previously noted, the thyroidal uptake of radioiodine measures the avidity of the gland for iodine, which is assumed to be proportional to the rate of production and secretion of thyroid hormone. For many years the percentage of thyroidal uptake at 24 hours has been the most widely used isotopic procedure for the estimation of thyroid function. The 24 hour thyroidal uptake, however, may lead to erroneous conclusions in those hyperthyroid patients in whom the metabolism of the I^{131} and its secretion in thyroid hormone is markedly accelerated. The maximum uptake of I^{131} may have occurred considerably earlier and, as a result of its release in thyroid hormone, may have decreased at 24 hours to a high normal level. The percentages of thyroidal uptake of I^{131} in patients with normal and abnormal thyroid function at 6 and 24 hours are given in table 1. It should be noted that the maximum uptake in the hyperthyroid patient is reached within 6 hours after the

TABLE 1

PERCENTAGES OF THYROIDAL UPTAKE OF I^{131} IN PATIENTS WITH NORMAL AND ABNORMAL THYROID FUNCTION

Diagnosis	*Time*	*Range*	*Mean*
Euthyroid	6 hrs.	7-25	14
	24 hrs.	10-50	23
Hypothyroid	6 hrs.	1- 7	4
	24 hrs.	<1-15	5
Hyperthyroid	6 hrs.	33-90	60
	24 hrs.	40-90	64

administration of the tracer dose. The obvious conclusion to be drawn from these data is that, as a screening test, the percentage of thyroidal uptake at 6 hours is more reliable than the 24 hour uptake. If the measurements are made at both 6 and 24 hours, those patients in whom release of the tracer dose as hormonal iodine is rapid will immediately become apparent. There is some overlap in the range of values for the 24 hour uptake in the euthyroid and hyperthyroid individual. The range in the euthyroid patient is 10 to 50% and in the hyperthyroid patient it is 40 to 90 per cent. At 6 hours this overlap does not exist, as the range of euthyroid function is 7 to 25, whereas that for hyperthyroid function is 33 to 90. A similar relationship also exists between the ranges at 6 and 24 hours for euthyroid and hypothyroid function. This is of less importance and significance, because generally the thyroidal uptake of radioiodine is not considered to be especially useful in the diagnosis of hypothyroidism.

Technic. The thyroidal radioiodine uptake is a relatively simple technical procedure requiring no preparation and a minimum of patient participation. A 5 to 20 μc tracer dose, usually in capsule form, is given by mouth and at a predetermined time, usually 6 and/or 24 hours later the percentage of this dose present in the thyroid is determined by a few minutes of external counting with a scintillation detector. The I^{131} employed in this test has a physical half-life of 8 days and is administered in the chemical form of NaI (sodium iodide). Since it is a fission product of uranium, U^{235}, and at no time existed as stable iodine, all of the iodine administered is in the form of I^{131}. Thus, it is carrier-free. The amount of iodine is 0.00805 μg per μc. Such a minute quantity of iodine can obviously have no biologic effect on the individual nor any effect on subsequent laboratory tests, such as the protein-bound iodine (PBI.). The radiation dose to the thyroid and whole body including the gonads from the small tracer doses of radioiodine employed in the measurement of thyroidal uptake is insignificant.

Conditions in Which the Thyroidal Uptake of Radioiodine Is Above Normal

An elevated thyroidal uptake of radioiodine is unfortunately not unequivocal evidence of hyperthyroidism. There are other thyroid abnormalities and physiologic and nutritional deficiency conditions in which the thyroidal uptake of radioiodine may be above normal. The administration or withdrawal of certain medications may also result in an increased uptake of radioiodine.

Those conditions in which the thyroidal uptake of radioiodine is above normal may be summarized as follows:

I. *Thyroid Abnormalities**
- Hyperthyroidism
- Iodine deficient goiter
- Cretinism with congenital goiter

II. *Physiologic Thyroid Hyperfunction*
- Pregnancy (after 6th week)

III. *Extrathyroidal Factors*
- Endogenous
  - Nutritional iodine deficiencies
  - Chronic alcoholism
  - Chronic liver disease (cirrhosis)
  - Low sodium diets
- Exogenous
  - Technical errors in measurement procedures
  - Residual I^{131} from previous (unknown) administration
- Medications
  1. Direct effect
     - Thyroid-stimulating hormone (TSH.)
  2. Indirect effect
     - Thyroid substances
       - Desiccated thyroid (4 weeks after cessation of therapy)
       - Thyroxin (T4) (3 to 4 weeks after cessation of therapy)
       - Tri-iodo-thyronine (T3) (5 to 10 days after cessation of therapy)
     - Adrenal steroids (2 to 7 days after cessation of therapy)
     - Antithyroid drugs
     - Antituberculosis drugs
     - Cobalt (after several months of therapy)

*May also be elevated in a small percentage of euthyroid patients after:
Surgical thyroidectomy
Radioiodine thyroidectomy.

A few of the conditions summarized above deserve some comment. The chronic alcoholic and patients with cirrhosis generally consume diets that are deficient in many aspects, one of which often is iodine. The thyroid glands of these patients are literally starved of iodine and, thus, have an increased avidity for this element. The chronic alcoholic often has symptoms such as tremors, weight loss, and tachycardia, which are common to hyperthyroidism. Extreme caution must be exercised in ascribing an elevated uptake in such an individual to hyperthyroidism.

Conditions in Which the Thyroidal Uptake of Radioiodine Is Below Normal

The 6 or 24 hour thyroidal uptake of radioiodine may be below normal in patients with organic thyroid abnormalities such as hypothyroidism, athyreotic cretinism, and thyroiditis. Decreases in thyroidal uptake of radioiodine may be due to a number of causes not associated with organic disease of the thyroid. These extrathyroidal factors may either influence the results of the physical measurements of the I^{131} in the gland or physiologically alter the affinity of the normal gland for I^{131}. These extrathyroidal factors are the most prevalent sources of incorrect results and subsequent misinterpretations of the thyroidal uptake test. The following is a summary in outline form of the more common conditions in which the thyroidal uptake of radioiodine is below normal.

I. *Thyroid Abnormalities*
   1. Hypothyroidism (primary)
   2. Cretinism (athyreotic)
   3. Thyroiditis

II. *Extrathyroidal Factors*
   1. Endogenous
      a. Deficiency of TSH. (secondary hypothyroidism)
      b. Vomiting of tracer dose
   2. Exogenous
      a. Failure to take tracer dose or to administer it
      b. Technical errors in measurement procedure
      c. Medications
         Iodides
            Inorganic
            Organic
         Thyroid substances
         Antithyroid drugs
         Miscellaneous drugs

Of the factors listed above, medications taken or administered prior to the performance of the radioiodine uptake test constitute the largest source of error. It is absolutely essential that physicians who utilize the radioiodine uptake test be familiar with those drugs and substances which influence the thyroidal uptake of radioiodine. They must also ascertain that the patient has not taken any of these medications before the uptake study is made. If the patient has taken these medications, the physician must be certain that sufficient time has elapsed since cessation of the medication in order to validate the results of the uptake measurements. Table 2 lists those medications or substances which influence the thyroidal uptake of radioiodine, the direction in which thyroid response will be altered, and the suggested waiting period after discontinuance of the substance before the uptake test is made. The list in table 2 is not complete, but from the experience of the author and others includes those agents most likely to be encountered in practice.[1]

The absence of certain substances and medications from the list in table 2 should be recognized. These are iodized salt, tranquilizers, and the radiopaque dyes used in retrograde pyelography. Iodized salt taken in normal dietary quantities does not constitute a sufficient intake of iodine to block the uptake of a tracer dose of I^{131}. Newman and Fish[2] showed that therapy with tranquilizers of the promazine, meprobamate, hydroxyzine, or reserpine type does not alter the results of thyroid function tests including the radioiodine uptake.

Radioiodine Secretion Tests

As was previously noted, the rational of estimating thyroid function on the basis of the percentage uptake of a tracer dose of radioiodine by the thyroid is based on the assumption that there is a direct corollary between the avidity of the gland for iodine and subsequent secretion of thyroid hormone. However, frequently there is a disassociation between the uptake of iodine and release of hormone. Therefore, it is useful to have available a clinical laboratory procedure to measure the secretion of the tracer dose in the form of thyroid hormone. From such a test

TABLE 2

COMMONLY USED MEDICATIONS AND SUBSTANCES WHICH INVALIDATE THE THYROIDAL I^{131} UPTAKE TEST

Medication or Substance	*Effect on Uptake*	*Recommended Waiting Period After Discontinuation**
IODIDES		
Inorganic		
Saturated solution K1 or Lugol's solution	Decreased	30 days
Hyperthyroidism		7 days
Tincture of iodine	Decreased	30 days
Cough medicines (syrup hydriodic acid)	Decreased	30 days
Vitamins containing more than 0.15 mg. iodine	Decreased	15 days
Some cod-liver oil preparations (iodine containing)	Decreased	15 days
Mineral supplements and health foods containing more than 0.5 mg. iodine daily	Decreased	30 days
Seafoods in large amount	Decreased	15 days
Organic		
Iodinated radiopaque dyes for radiographic contract media employed in:		
Cholecystography		
Telepaque	Decreased	1 month—indefinite
Priodax	Decreased	1 month—indefinite
Cholegrafin	Decreased	1 month—indefinite
Urography		
Diodrast	Decreased	30 days
Neo-Iopax	Decreased	30 days
Urokon	Decreased	30 days
Angiocardiography and other angiographies		
Hypaque	Decreased	30 days
Bronchography		
Lipiodol	Decreased	2 years—indefinite
Iodochlorol	Decreased	2 years—indefinite
Dionosil	Decreased	30 days
Myelography	Decreased	4 weeks—indefinite
Pantopaque		2 years—indefinite
Salpingography		
Skiodan Acacia	Decreased	30 days
Salpix	Decreased	30 days
Iodinated amebicides (chiniofon, iodochlorhydroxyquin, diiodohydroxyquin)	Decreased	30 days
Vaginal suppositories (floraquin, diiodohydroxyquin)	Decreased	30 days
Skin ointments (vioform)	Decreased	30 days
Tridihexethyliodide (Pathilon)	Decreased	30 days
Penicillin G [Neo-Penil (diethylaminoethyl ester hydriodide)]	Decreased	15 days
THYROID SUBSTANCES		
Thyroid desiccated	Decreased	40 days
(4 weeks after cessation of therapy)	Increased	
Thyroxin (T4)	Decreased	40 days
(3 to 4 weeks after cessation of therapy)	Increased	
Tri-iodo-thyronine (Cytomel, T3)	Decreased	21 days
(5 to 10 days after cessation of therapy)	Increased	
ANTITHYROID DRUGS		
Thiourea and methimazole		
In euthyroidism or controlled hyperthyroidism	Decreased	30 days
In uncontrolled hyperthyroidism	Decreased	2 days
Iodinated thiouracil (Itrumil)		
In euthyroidism or controlled hyperthyroidism	Decreased	30 days
In uncontrolled hyperthyroidism	Decreased	15 days
MISCELLANEOUS DRUGS		
Thyroid-Stimulating Hormone (TSH.)	Increased	4 days
Adrenal steroids	Decreased	7 days
Antituberculosis drugs (PAS, INH)	Increased	30 days
>3 months therapy		
Cobalt (hematinic)	Increased	30 days
>3 months therapy		
Bromides	Decreased	30 days
Acetazoleamide (Diamox)	Increased	3 days
Thiocyanate	Increased	5 days
Perchlorate	Increased	7 days
Butazolidin	Decreased	7 days

*In general, it can be assumed that the longer the period of ingestion, the longer the waiting period.

indirect evidence of the rate of synthesis of thyroxin by the gland is also obtained. In the previous outline of clinical procedures, two secretion tests were noted, namely, the plasma protein bound I^{131} (PBI^{131}) and the conversion ratio between PBI^{131} and total plasma I^{131}. The latter test originally described by Clark[3] is a valuable aid in the diagnosis of hyperthyroidism, especially in those cases in which the tracer dose of I^{131} is rapidly utilized by the gland in the synthesis of thyroxin and secreted into the blood in less than 24 hours. This will often lower the apparent 24 hour uptake into the upper euthyroid range. It may also be employed to confirm an impression that an elevated iodine uptake is the result of an increased "iodine space" and not due to hyperfunction of the gland. It is likewise useful in those patients who have had either surgical or radiation thyroidectomy and who persistently have elevated iodine uptakes, but who are clinically euthyroid. It is thought that the elevated thyroidal uptakes in this group of patients is due to a high percentage of utilization by the gland in an abortive attempt to produce thyroxin (T4) which results in the secretion of T1 and T2.

Conversion Ratio Procedure. The methodology for the determination of the conversion ratio is considerably more complicated than the direct measurement of the thyroidal uptake of radioiodine. It also has the disadvantage of necessitating the administration of a much larger tracer dose, 50 to 100 μc of I^{131}. The methodology may be summarized as follows.

1. Plasma is separated from sample of venous blood taken 24 hours after oral tracer dose of 50 to 100 μc I^{131}.
2. I^{131} radioactivity in plasma is determined. (Summation of PBI^{131} and inorganic I^{131}.)
3. Protein-bound iodine separated from plasma by:
   a. Precipitation with trichloracetic acid, or
   b. Passage of plasma over anion exchange resin.
4. I^{131} radioactivity of PBI^{131} determined.

$$\text{Calculation conversion ratio (\%)} = \frac{\text{Radioactivity as } PBI^{131}}{\text{Total radioactivity in plasma}} \times 100\%$$

Ratio >50% = hyperthyroidism

The conversion ratio gives consistent results and is a reliable procedure for the diagnosis of hyperthyroidism. The test is not reliable for differentiation between euthyroidism and hypothyroidism.

Modified Uptake Procedures

Tri-iodo-thyronine Suppression Test. In those patients in whom an uptake in the equivocal range of 40 to 50% has been found and in whom there has been sufficient clinical evidence upon which to definitely establish the absence or presence of thyrotoxicosis, clarification of the significance of the percentage of thyroidal uptake can usually be obtained by the performance of the Cytomel (T3) suppression test originally described by Werner.[4] In the euthyroid patient the administration of exogenous thyroid hormone will suppress the subsequent uptake of radioiodine to less than 20% of the tracer dose. In hyperthyroidism, however, there may be no suppression of the uptake after thyroid hormone or, if suppressed, it will not be to a level less than 35% of the tracer dose. Tri-iodo-thyronine (T3) is generally employed instead of thyroid extract, because of the rapidity of its action and dissipation. The procedure for this test is as follows.

1. Perform standard 24 hour uptake.
2. Administer 75 μgm of T3 (Cytomel) orally each day for one week.
3. Administer second tracer dose of I^{131} and measure the thyroidal uptake.

In the euthyroid patient the second uptake is suppressed to less than 25% and is usually suppressed into the hypothyroid range. In thyrotoxicosis the second uptake is not suppressed below 35% and, in some instances, is not suppressed at all.

TSH. Stimulation Test. In patients with clinical and laboratory evidence of hypothyroidism and in whom it is not possible to determine whether or not this is secondary to hypopituitarism, the indecision can be resolved by the performance of the radioiodine uptake test 48 hours after the injection of 5 USP. units of thyroid-stimulating hormone (TSH.). In primary hypothyroidism the gland is incapable of responding to TSH. and there will be no significant increase in the iodine uptake following such stimulation, but in hypothyroidism due to a deficiency in the

secretion of TSH. by the pituitary there will be a significant elevation in the uptake of radioiodine after TSH. Failure of the gland to respond to TSH. is conclusive evidence of primary hypothyroidism. A positive response, however, will not differentiate the euthyroid patient whose uptake was originally in the low range of normal from one with secondary hypothyroidism.

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II. Therapeutic Considerations in the Use of Radioiodine in Thyrotoxicosis*

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PREVIOUS DISCUSSIONS in this Symposium have included information on the nature of, and the mode of action of a radioactive isotope. With special reference to the use of radioiodine-131, we are fortunate indeed in the possession of a unique tool. The thyroid gland will concentrate radioiodine approximately 200 times its concentration in serum; it will do this rapidly and will store radioiodine in the thyroid cell and in the follicle. Approximately 90% of the radiation is beta radiation which travels a scant 2 or 3 mm. through human tissues so that virtually none of the tissue outside the thyroid capsule is subjected to beta radiation. The remaining 10% is gamma radiation which makes its presence felt in the adjacent tissues. It is this gamma radiation which allows us to do external counting. By virtue of these unique physiologic qualities, one may place radiation where it is needed and permit only negligible radiation to tissues outside the gland. Since the gland cannot distinguish between stable iodine and radioiodine, the uptake and retention of radioiodine allows for bombardment of the thyroid cell and even suicide of the thyroid gland if enough radiation is given to the gland.

Despite the fact that two decades have passed since the introduction of radioiodine in the treatment of hyperthyroidism, one still encounters confusion and even hostility to its use. Part of this may be explained on ignorance of the material, the dose level to be given and the possible bad sequelae following the use of radioiodine. It may not be amiss to make some statement with reference to the average treatment dose level. The amount of radioiodine in the average treatment dose approximates 0.02 micrograms of iodine; this dose level is approximately 1/50,000 mg. of iodine. This information immediately answers the question with reference to whether a tracer dose does or does not interfere with the protein-bound iodine estimation in blood; obviously it will have no effect on a PBI. estimation. A second question that is answered is the question of treatment of a patient who is sensitive to iodine. Obviously, 1/50,000 mg. of iodine will not cause symptoms even in a very sensitive patient. Fear of sterility as a result of exposure to radioactive isotope is common, not only in patients, but in hospital personnel. From time to time we have been timidly asked the question by the attending staff, as to whether or not there is danger of sterility from exposure to radiation. There is ample evidence at this time that the dose levels used in the treatment of thyrotoxicosis cannot and will not induce sterility. It cannot be associated with reasons for skipped menstrual periods in a female attendant on a case that has been given radioactive iodine. It is well known that thyrotoxicosis itself may cause

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sterility. Actually, treatment with radioiodine of the thyrotoxicosis, and control of the thyrotoxicosis may allow for normal pregnancy and delivery of a healthy offspring. As a matter of fact, many pregnancies have been achieved and healthy offspring delivered in patients who previously had sterility and uncontrolled thyrotoxicosis.

Treatment of Thyrotoxicosis

Three methods of control of thyrotoxicosis are available to the clinician today. These include antithyroid drug therapy, surgical management and the use of radioiodine. It is generally conceded that thyroid blocking drugs have been disappointing in the ultimate control of thyrotoxicosis. This is occasioned by the high rate of recurrence of thyrotoxicosis, the possibility of hematologic complications, the incidence of drug allergy and the nuisance of continued close check upon the patient. In the majority of instances one is left with the choice of surgical management versus the use of radioiodine.

In the consideration of these two forms of treatment, one must agree as to the relative risks of the two methods. The risk involved in surgical intervention is the possibility of death or a disabling illness involving abnormality of thyroid function, partial or complete paralysis of the vocal cords, thyroid storm, hemorrhage, pulmonary embolism, and the like. The extent of hypothyroidism following operation approximates that following radioiodine treatment. If the surgical mortality rate in a given locality is greater than 0.5%, there seems little good reason for entertaining the surgical management. In many areas of this country the operative mortality in Graves' disease is greater than 3 per cent. Even dealing with the lower mortality rates, one should not forget that for the unfortunate dead patient, the mortality is 100 per cent. Pregnancy constitutes a definite contraindication to the use of radioiodine because it traverses the placenta and may impair the fetal thyroid. Pregnancy cases complicated by thyrotoxicosis are best managed by the judicious use of antithyroid drugs with or without surgery.

There is really only one major objection which may possibly be laid at the door of the use of radioiodine for the management of thyrotoxicosis. This major objection is the possible development of malignancy following radiation. Whether radioiodine treatment for thyrotoxicosis may have a carcinogenic effect is a much debated issue. Basically, most of the data obtained on laboratory animals do indicate that large doses of radioiodine may produce tumor-like growths in rats and mice. Less well known is the fact that this effect may be largely controlled if desiccated thyroid is used in the post-treatment period. Positive statements for humans cannot as yet be made about the ultimate results of thyroid radiation with radioiodine. It can be said that up to this time there are no convincing data that such treatments have ever produced cancer in the human thyroid. This is surprising indeed, because sooner or later a pre-existing carcinoma in a thyrotoxic gland will manifest itself for the first time in the post-treatment period; when it does it will surely be blamed on the treatment. In a recent communication from Dr. Sidney Werner, it was pointed out that there are only 12 known cases of leukemia which occurred following radioiodine treatment of thyrotoxicosis. An international survey is now in progress to determine the total number of leukemia cases in relation to the total number of cases treated with radioiodine for thyrotoxicosis. It is important to know whether this number exceeds the number that would be expected purely by chance. It has been asserted that some 20 or 30 years must elapse after radiation before evaluation of possible development of malignancy can be ascertained. Approximately 20 years have elapsed since treatment with radioiodine for thyrotoxicosis was started; it may still be too early to assess the final results. With each passing year since 1940, there has been increasing security in the feeling that radioiodine treatment for thyrotoxicosis does not induce malignant change in residual thyroid tissue in human beings.

What may be expected as a result of treatment of thyrotoxicosis with radioiodine? In a recent review of the literature, Cassidy and Astwood,[1] assessing some 4,500 collected cases from the literature treated with radioiodine, indicate that the control of hyperthyroidism may be obtained in two thirds of the cases with a single dose and in 90% of the cases with two doses. Approximately 10% of the patients will require three or more doses. There can be no failure to control thyrotoxicosis in the sense that every case of hyperthy-

roidism can be controlled by this method alone if the administered dose is adequate. There is no mortality, paralysis of the vocal cords, hypoparathyroidism or postoperative complications. Because of these considerations one may realize the superiority of radioiodine therapy.

A less important complication of treatment is the incidence of transient and permanent hypothyroidism following treatment. The over-all literature indicates an incidence of approximately 12% of cases requiring the administration of thyroid substance to control symptoms of hypothyroidism. This figure compares favorably with hypothyroidism following operation which is radical enough to control recurrent hyperthyroidism and constitutes a true subtotal thyroidectomy. As indicated above, this objection is not serious since the symptoms are readily controlled by orally administered thyroid substance. There are, however, certain features of interest in relation to the appearance and development of hypothyroidism. Most of the cases occur after average or low doses of radioiodine approximating 7 millicuries in a single dose. The perplexing feature is that the dose level used is no larger than the dose level which will induce a state of euthyroidism in the majority of cases.

There seems to be no method extant for predicting the ultimate effect upon thyroid function whether the dose is calculated on estimated half-life, gross or accurate estimate of gland size, etc. It is generally agreed that larger glands require larger doses but gross exceptions to this have been observed. In general we have used 4 millicuries for normal size glands, doubling this dose for glands twice normal in size. It is barely possible, as we have previously suggested, that there is a biologic variation in sensitivity to radiation for which we do not have at this time an adequate measuring stick. It has been suggested that antithyroid drugs given soon after treatment interfere with the effectiveness of the treatment dose. These views have recently been challenged by Cassidy and Astwood, who found significantly smaller incidences of hypothyroidism if the radioiodine treatment was followed by the administration of antithyroid drugs. We have always administered antithyroid drugs in cases we have treated. These drugs are administered for 4 to 6 weeks following radioiodine administration.

In view of the above considerations, it is our studied feeling that radioiodine is a treatment of choice for Graves' disease. There exists considerable reluctance in many quarters toward the administration of radioiodine to patients under 25 years of age. This reluctance is, of course, predicated on the possible development of malignancy in later years. The next decade should see the determination of the safety or lack of safety in radioiodine administration.

With reference to nodular glands, the feeling is mixed as to whether or not such patients should have surgical intervention rather than radioiodine treatment. Two considerations enter into the decision, namely, that nodular glands have a higher incidence of malignancy, and nodular glands that are the seat of cysts and calcific changes do not diminish significantly in size following treatment. All one can say at this time is that if the gland is the seat of cystic degeneration and calcification, and affords mechanical obstruction, operation is the method of choice. It may be desirable to control thyrotoxicosis with radioiodine before resorting to surgery. In defense of the use of radioiodine in the toxic nodular glands, it may be said that many of these cases evince abnormality of cardiac rhythm or impairment of the cardiovascular system. In general, they are in the older age group and poor risks from the surgical standpoint. On the other hand, they are often more difficult to control with single doses than are cases of Graves' disease.

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Radiological Uses of Radioactive Materials*

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IN MANY HOSPITALS and clinics the radioisotope laboratory is organized as a division of the Department of Radiology. Under this arrangement, it is especially advantageous to combine this important facility with the section of therapeutic radiology in order to utilize the services of a radiation physicist more efficiently. Regardless of who is practicing this new specialty of nuclear medicine, a good knowledge of clinical medicine, pathology and radiation physics is required.

Iodine-131 is the most frequently used radioisotope by the medical profession today. Its use in thyroid evaluation and treatment has been covered by others on this program. My allotted time does not permit detailed coverage of all the diagnostic and therapeutic procedures which can be done in the well-equipped clinical isotope laboratory, but I shall try to briefly cover those most frequently employed by the radiologist.

Diagnostic

Of the numerous applications of radioisotopes in the practice of radiology, one of the most informative concerns diagnosis and localization of tumors. The two isotopes most frequently used for this work are iodine-131 and phosphorus-32. Both have relatively short half-lives (iodine 8 days and phosphorus 14 days) and therefore can be safely used at diagnostic levels. The gamma ray emissions of I^{131}, in addition to its beta ray, makes it useful for external counting technic such as is used in brain tumor diagnosis and localization. The use of P^{32} is limited to internal or contact technic since it emits beta radiation only which has a range within tissues of about 8 mm.

We have found iodinated human serum albumin (I^{131} H. S. A.) useful as a screening process to aid in selection of patients for further diagnostic studies such as carotid arteriography and ventriculography. Illustrative is the case of a 50 year old white man who entered the hospital in a semicomatose condition. He had previously undergone a lobectomy for bronchogenic carcinoma and therefore cerebral metastasis was suspected. There were no localizing symptoms or signs on neurologic examination. Twenty-four hours following intravenous injection of I^{131} H. S. A., a gammagram of the left cerebral hemisphere showed an area of localized radioactivity in the parietal area. With this information, a left carotid arteriogram was performed and confirmed the location of the tumor. This area was then treated with cobalt-60 teletherapy and remarkable improvement resulted. He regained consciousness and was ambulatory when discharged.

Iodine-131 in the form of sodium iodide given orally 24 hours prior to operation for thyroid cancer is useful in checking on the completeness of thyroidectomy, as small areas of concentrated I^{131} can be detected with a miniature beta-gamma sensitive probe. These areas might otherwise have been overlooked. Although the percentage of metastatic thyroid cancer lesions capable of picking up iodine is small, it is possible to detect bone metastasis in some cases before sufficient destruction has occurred to make them visible on roentgen examination.

Phosphorus-32 in the form of sodium phosphate is generally given intravenously for diagnostic purposes in amounts up to 1 millicurie. Its value as a diagnostic tool is due to its being taken up by rapidly metabolizing tissues. Thus, malignant breast tumors and metastatic lesions show at least 25% greater activity than corresponding normal areas 24 to 48 hours after administration of the isotope.

It has been demonstrated that there is a high differential uptake of P^{32} in most brain tumors. Studies have indicated that tumor tissue will absorb from 5 to 100 times the

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activity of similar specimens of normal brain tissue. A needle size Geiger counter can be probed into various areas of the brain during operation to determine the areas of highest concentration. Deeply-seated tumors can be located by this technic and a high counting differential between normal tissue and tumor aids in determining completeness of removal.

The identification of malignant tumors of the eye, for which histologic examination is only possible after enucleation, is a most important use of P^{32}. When carefully done, this test should decrease the incidence of enucleation for suspected malignancy which histologically proves to be benign. The major problem in identification of intraocular tumors is that of differentiation between detachments of the retina caused by underlying fluid, benign inflammatory condition or malignant growth. P^{32} is given intravenously in doses up to 1 millicurie, and by using a specially designed Geiger probe counts are made over the suspected area of the tumor and over the corresponding position in the normal eye. Benign tumors, hemorrhages and cysts yield normal or even subnormal ratios. Peak ratios in inflammatory conditions average 1.33 and fall rapidly as compared to tumors which retain a high ratio of counting for periods extending into days.

Another useful diagnostic application of P^{32} is as an indicator of the blood supply to the femoral head following fracture of the neck of the femur. Following an intravenous dose of sodium P^{32}, the radioactivity of a segment of bone from the femoral head and from the intertrochanteric portion can be compared at operation. An impaired blood supply results in decreased radioactivity.

Therapeutic

The radiation therapist now has at his disposal new sources of beta and gamma radiation to supplement his use of x-rays and radium. Radiation treatment of the thyroid is not new but the selective absorption of radioactive iodine with its resultant beta and gamma irradiation is. While the radiologists' greatest use of radioactive material is for treatment of toxic goiter and metastatic thyroid carcinoma, details of the management of hyperthyroidism have already been presented.

Radioactive iodine is not the treatment of choice for carcinoma of the thyroid gland. The best available single therapeutic measure today for this condition is surgery. For all general purposes, no patient should have I^{131} for treatment of thyroid carcinoma without at least a surgical biopsy. Although x-ray therapy has proved disappointing, its effect has been much more thoroughly evaluated over a longer period of time than has the use of I^{131}. Consequently, we advise x-ray therapy whenever a total thyroidectomy has been carried out with or without a radical neck dissection, and evidence is found for reasonable suspicion that thyroid carcinoma still remains in the cervical lymphatics but is not present in other areas of the body. The use of x-ray therapy is also advised in preference to I^{131} in obvious inoperable thyroid carcinoma, very rapidly growing where biopsy reveals small or large cell carcinoma or lymphosarcoma of the thyroid. The chief indication for I^{131} is in the treatment of metastatic lesions, if they can be made to concentrate the isotope and also to complete the job that the surgeon started, namely, a total thyroidectomy for the removal of all normal and cancerous thyroid tissue. Less than 50% of carcinomas of the thyroid have been demonstrated to pick up measurable amounts of radioactive iodine. Generally, when the histologic section shows that the carcinoma produces colloid, the carcinoma will concentrate I^{131}. If the neoplasm does not exhibit colloid it will not concentrate I^{131}. Approximately one third of the papillary carcinomas are able to concentrate radioiodine.

Currently radiophosphorus is used most extensively in the therapeutic management of polycythemia vera and chronic leukemia. It should be emphasized that P^{32} does not accelerate destruction of circulating red blood cells. The effect is confined to suppressing hematopoiesis in bone marrow. The red blood count does not begin to fall for 3 or 4 weeks after the initial injection. Symptomatic improvement occurs in over 90% of patients treated. In 95% of patients a significant reduction in the size of the spleen may be expected, and reduction in the size of the liver occurs in more than one half of the patients treated. Remissions as long as 4 years have been reported and life expectancy has been increased so that most patients live from 5 to 25 years after the onset of symptoms, with a median survival of 13.2 years.

In treatment of the leukemias, radiophos-

phorus, like x-ray, is of little value in acute cases. Roentgen irradiation is valuable in chronic leukemias for the management of localized leukemic infiltration, such as in the spleen. In predominantly generalized involvement, however, radioactive phosphorus is of superior value. Results of treatment show that radiophosphorus is more effective in chronic granulocytic leukemia than in chronic lymphocytic leukemia.

In most instances the response of the various lymphoblastomas has been less favorable to radiophosphorus than to roentgen therapy or nitrogen mustard and related chemotherapeutic agents. The best results thus far with radiophosphorus have been obtained in treatment of lymphosarcoma, including the related conditions of giant follicular lymphoma, and mycosis fungoides.[1-3] When the disease is widespread and local roentgen therapy is no longer feasible, intravenous radiophosphorus may be beneficial.

Radiophosphorus is inferior to x-radiation in the treatment of Hodgkin's disease.[1] Nitrogen mustard and local roentgen therapy appear to be more generally effective. Myelomatous tissue does not concentrate radiophosphorus sufficiently to warrant its use in the treatment of multiple myeloma except in extremely radiosensitive cases. It does, however, bring about relief of bone pain in most cases, although the radiologic appearance of the lesions remains unchanged. Local roentgen therapy is preferable for solitary myeloma.

Maxfield[4] has recently reported the use of radiophosphorus combined with testosterone in the treatment of metastatic bone lesions from carcinoma of the breast and prostate. Concurrent administration of testosterone increases the uptake of radiophosphorus by the bone metastasis and results in more effective delivery of therapeutic doses of irradiation to the malignant cells. More than 90% of patients treated in this manner experience relief of pain and amelioration of symptoms; 15% exhibit osteoblastic repair and a few, return of normal bone structure.

Many radioisotopes can be prepared in the form of colloidal suspensions. The most frequently employed colloidal substances are radioactive gold (Au^{198}) and radioactive chromic phosphate (P^{32}). A third substance, radioactive yttrium (Y^{90}), has also been proposed for radiocolloid therapy. These isotopes can be administered in three ways: intravenously, interstitially, by direct infiltration into tumors, and by injection into the large natural body cavities, i.e., intraperitoneal and intrapleural administration. The radiocolloids are insoluble and biochemically inert. Their distribution depends upon mechanical transport by the phagocytic cells of the reticuloendothelial system and this, in turn, depends largely on the route of administration. When radiocolloids are injected interstitially into tumors or body tissue, they tend to remain *in situ*, near the site of injection. A small amount of the material may be engulfed by phagocytes and carried by way of lymphatic channels into the blood stream. Intracavitary colloids are deposited unevenly on the surfaces of the cavity. A small variable amount also reaches the lymphatics and the blood stream. Intravenously injected radiocolloids are rapidly removed from the circulation by phagocytes in the reticuloendothelial system, especially by those in the liver and to a lesser degree by those in the spleen and bone marrow.

Intracavitary radiocolloid therapy for recurrent malignant effusions of the serous body cavities is indicated whenever paracenteses or thoracentheses are required more frequently than once every month. It is restricted to effusions in which malignant cells have been demonstrated in centrifuged specimens of intracavitary fluids. These agents are of no value in the treatment of nonmalignant effusions. Radiocolloids seem to be of prophylactic value following operation for carcinoma of the ovary, particularly in early cases. Instillation is made either at the time of laparotomy or as soon thereafter as feasible. Extensive papillary carcinoma of the urinary bladder has been successfully treated by direct instillation of radioactive gold directly into the urinary bladder. The usual treatment is to instill approximately 300 millicuries of radiogold and allow it to remain within the bladder for a period of 3 hours. It is then withdrawn and the bladder thoroughly rinsed with normal saline. Calculated on the basis of 150 ml. volume, the bladder wall receives approximately 3,000 rads.

The interstitial injection of colloidal suspensions of radioisotopes makes it possible to deliver very high doses of radiation to the

tumor and relatively little radiation to the adjacent normal tissue. Unfortunately, the intratumor distribution of these agents is extremely variable. Flocks and associates[5,6] have reported excellent palliative results following the injection of radiogold into malignant tumors of the prostate. For carcinoma of the cervix the parametrial areas have likewise been successfully irradiated by interstitial injection of radioactive gold through the paracervical mucosa into the parametrium.

Intravenous therapy of chronic myelogenous leukemia with gold-198 has been tried but the life expectancy of the chronic leukemia patient has not been materially affected by this agent. Clinical results obtained with intravenous radiogold therapy and chronic leukemia include: a reduction of white blood count and a return of a relatively normal differential white cell distribution; reduction of splenomegaly, hematomegaly and lymphadenopathy; loss of anorexia, followed by increased sense of well-being and weight gain; and in satisfactory remissions an increase in hemoglobin and erythrocyte levels. Intravenous radioactive chromic phosphate seems to be most efficacious in chronic lymphatic leukemia, especially in those cases which have become resistant to x-ray and radiophosphorus.[7]

Radioactive cobalt was first employed as a replacement for radium in interstitial implantation therapy in permanently loaded needles. Nylon sutures containing small cobalt-60 sources are a more flexible type of individualized applicator for implantation therapy, and are easily removable from both external and intracavitary locations. Radioactive gold seeds have exactly the same appearance and dimensions as radon seeds but their only advantage over radon appears to be uniformity in strength. A solid source of cobalt-60 placed within the center of a balloon bag catheter is used for intracavitary therapy of cancer of the urinary bladder. It can successfully destroy lesions which are not infiltrating and is particularly valuable in the treatment of multiple noninfiltrating tumors. Infiltrative lesions are best treated by a combination of surgery and interstitial cobalt-60 containing sutures. In far advanced cases intracavitary radiation may have a palliative effect and may control persistent bleeding. Cobalt-60 has also been used in a liquid form in which it is directly injected into the rubber bag to inflate the catheter and allowed to remain in the urinary bladder until a cancerocidal dose of radiation is delivered.

Because of the limited penetration of beta rays, contact therapy with an applicator such as strontium-90 applicator will deliver little radiation to deeper structures. This is especially useful in treating superficial diseases of the eye where it is undesirable to irradiate the lens. The strontium-90 applicator has been most valuable in controlling vascularization before and after keratoplasty. Pterygia can be treated directly when the lesions are thin and relatively new. Corneal ulcerations and papillomata respond exceptionally well. The strontium-90 applicator is occasionally used for treatment of small skin lesions, usually those of less than 1 cm. in diameter. It is particularly useful in the treatment of hyperkeratotic lesions.

Large sealed sources of cobalt-60 and cesium-137 are presently being used extensively as teletherapy sources. Treatment with these sources has certain very definite clinical advantages. There is decreased skin reaction, since maximum ionization occurs 6 mm. below the skin surface. Depth dose is higher because there is less attenuation in the skin and intermediate tissue. Absorption in bone and cartilage is no higher than in soft tissues; thus the possible necrosis of bone or cartilage is minimized when adjacent lesions are treated. Systemic reaction is milder since exposure of neighboring normal tissue is reduced, particularly in the treatment of deep-seated tumors in the thorax and abdomen. Indications for cobalt-60 or cesium-137 treatment are not fundamentally different from those for conventional deep x-ray therapy.

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The Radioisotopic Localization of Intracranial Neoplasia Utilizing the Focusing Collimator Scintillation Counter with Photoscan Attachment*

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MORE THAN A DECADE has passed since the first efforts were made to detect the presence of intracranial neoplasia by means of radioisotopes. In that period over 90 articles and two books have appeared in the world literature dealing with various technics of localization. The commonly employed isotopes have been iodine, potassium, phosphorous, arsenic, and copper. External and internal detecting devices have been perfected, and the simple Geiger-Müller tube has been replaced by the more sensitive scintillation detector. The reported results of accuracy of detection have varied from as high as 95% to as low as 10 per cent.

Moore's[1] initial investigations utilized radioactive diiodofluorescein as the tracer substance and the GM tube as the detector. Ashkenazy[2] and associates repeated Moore's work and claimed a 95% accuracy of detection. Belcher and collaborators[3] failed to substantiate these findings and concluded that, "the technique may prove to be a useful method of physiological investigation even if of little value in tumour localization." Many investigators in different clinics have since repeated the original work and have reported varying degrees of accuracy.[4-11] The single point of agreement among the early enthusiasts was the need for better instrumentation. The rapid progress which has been made in this field is due entirely to the development of ingenious complex electronic devices to permit accurate resolution and recording. The development of the pulse height analyzer and its adaptation to scintillation counting by Francis and co-workers[12] were major milestones. Wrenn and associates'[14] pioneer work in the use of the positron emitting isotopes and their further development by Brownell and Sweet[15] introduced a new concept in the scanning method. Many investigators have studied the internal method of brain tumor detection by means of fine probe counters for the localization of beta-emitting nuclides such as P^{32} at the time of craniotomy.[16,17]

Despite the many glowing reports of radioisotopic localization of brain tumors, it has been our experience that neurosurgeons in general have been reluctant to accept this ancillary method of diagnosis. When we began our pilot scanning studies there was considerable skepticism on the part of both physicians and surgeons which was not without justification. Although we began our studies with the best instrumentation commercially available, our initial attempts met with partial failure. Many modifications in the equipment had to be made by our physicist, Dr. James Mozley, before cerebral scans of good quality could be obtained. The essentials of satisfactory instrumentation for this procedure will now be briefly described.

Technic

Although sodium iodide (TL) scintillation crystals of small size suffice for thyroid and hepatic scanning, a larger, more sensitive crystal (3 inches in diameter and 2 to 3 inches in depth) must be used for cerebral scanning in order to keep the dose of radioactivity at a reasonably low level. The crystal, photomultiplier, and cathode follower are housed in a lead shield one and one-half to two

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inches in thickness, and a lead collimator 3 inches in depth is mounted below the crystal. This collimator has a series of tapered holes whose axes focus at a depth of 3 inches below the collimator surface. These serve to limit the gamma radiation "seen" by the detector to a limited volume within the skull, thereby improving resolution. Many different patterns for the number and distribution of these holes have been tried. In our experience the twelve hole sensitive-volume collimator developed by Shy and associates,[11] has been superior to all others, including the 61 hole Oak Ridge collimator, and the rather poor single-bore collimators.

The detector, mounted on the scanning frame is motor-driven, back and forth over the patient's head, at the rate of 5 inches per minute, until the entire skull area has been mapped out. The resultant scans are designated as right or left lateral, frontal or occipital projections depending upon the position of the probe in relation to the skull.

The precision-type of gamma spectrometer should be used for amplifying and analyzing the pulses from the detector. The so-called "medical spectrometer" with variable high voltage supply and analyzer is not stable enough for cerebral scanning where only small differences in counting rate exist between the normal brain and tumor tissue.

The pattern of the radioactivity is usually presented in the form of a dot pattern on paper by a mechanical solenoid tapper. Interpretation of the images, however, is much easier and more accurate if they are displayed on x-ray film by a photorecorder.[13,18] The photorecording attachment consists of a light-tight box containing a small light source which moves over the film as the detector moves over the patient. The gamma radiation is transformed directly into an electrical current, and the intensity of the light source is proportional to the count rate of the source. An alteration of the size of the aperture of the light or a variation of the distance from the unexposed film can alter the amount of contrast obtained. When the probe passes over a "hot" source such as a brain tumor, the film is exposed to a higher intensity of light and a dark spot is seen when the film is developed. Unfortunately, although good photorecorders have relatively simple electronic circuits, they are not yet commercially available.

We have employed radioiodinated serum albumin as the tracer in these studies. On the first day the patient is given 10 drops of Lugol's solution at 8 a.m. and again at 8 p.m. On the second day an intravenous injection of the isotope is made in the amount of 25 microcuries per 10 pounds of weight. On the third day scanning is performed.

The following photoscans with accompanying case histories represent examples of this technic at the present time. A series of 250 cranial scintillation scans have been performed to date. A second communication will discuss our statistical analysis of this group, as well as a detailed description of the modified instrumentation.

Case Illustrations

Figure 1,A represents a left lateral cranial scintillation scan in a normal individual. In the interpretation of the normal scan there are certain constant areas of increased specific activity which must be noted. The area of the temporalis muscle, indicated by the very dark rows, is the most striking. Frequently, depending upon the contrast, one may see areas of increased specific activity in the area of the superior longitudinal sinus, the torcular Herophili, and the lateral sinus. The last three areas are not constant, but should be considered as normal when present. In the frontal projection (Fig. 1,B) one notices a specific and constant area of increased specific activity, the source of which is the extraocular muscles. One may also see in this projection a normal area of increased specific activity in the region

FIG. 1, A

FIG. 1, B

of the superior longitudinal sinus. The latter varies considerably depending on the contrast setting.

Case 1. Figure 2 (A and B) represents scintillation scans of a 44 year old white, right-handed woman who was admitted for investigation of seizures of approximately 2 years duration. The seizures began in the right leg and progressed to a generalized tonic, clonic convulsion. Skull x-ray studies, electroencephalogram and ventriculogram, made at the onset of the attacks, were reported as negative. After 6 months there was a further appearance of seizures and another electroencephalogram and an air study were made and considered normal. The patient began to drag the right foot and develop an unsteady gait. A psychiatric explanation was sought for this symptomatology, and subsequent hospitalization was carried out.

FIG. 2, A

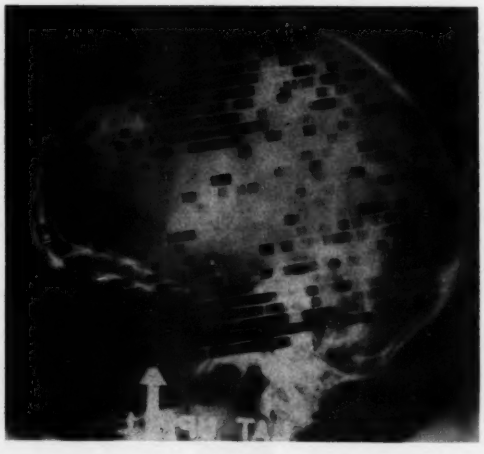
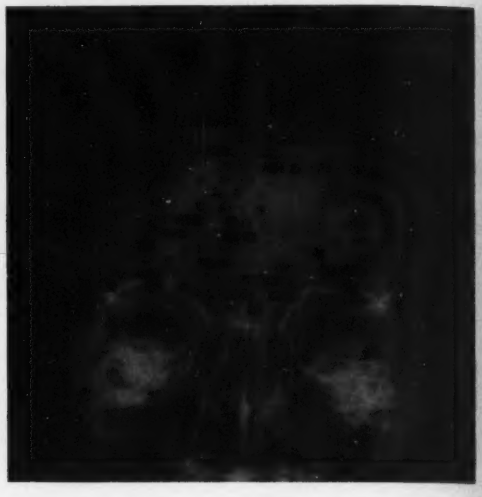


FIG. 2, B



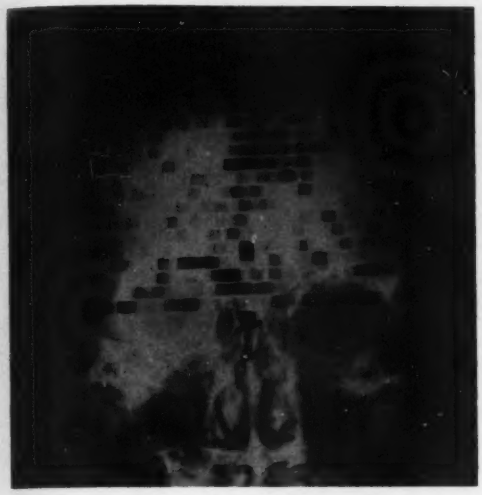
On admission to The Johns Hopkins Hospital the general physical examination was within normal limits. Neurologic evaluation revealed a minimal right hemiparesis. A left carotid arteriogram suggested a parasagittal lesion. The scans revealed a large parasagittal tumor which is well demonstrated on both the left lateral and frontal projections.

At operation the impression of parasagittal meningioma was confirmed.

Case 2. Figure 3 (A and B) shows the scans of a 64 year old white, right-handed man who was admitted to the hospital with the chief complaint of in-co-ordination of his left arm and leg of 6 weeks duration. He first noted this difficulty while walking up a hill when his legs seemed to be lagging. Over the interim period he noted that his left toe would catch on rugs and curbs. About 4 weeks prior to admission his left hand became weak and in-co-ordinated. He had difficulty in knowing where his left hand was unless he watched it.

FIG. 3, A

FIG. 3, B



The admission physical examination was found to be within the limits of normal. On neurologic examination the station was slightly unsteady and he was unable to walk heel-to-toe. Strength in the left leg was reduced in all muscle groups. The left arm was slightly spastic and weak. A left quadrantic homonymous hemianopsia was present. The left plantar response was extensor.

X-ray films of the skull were negative. A right carotid arteriogram failed to reveal a lesion. Ventriculogram showed a right posterior parietal mass lesion. The scan revealed specific abnormal activity in the parieto-occipital region in both the frontal and right lateral projections. One notes in the frontal projection (Figure 3,B) that the specific abnormal activity does not extend to the surface.

This fact was verified at subsequent operation, and a metastatic lesion was found in the area outlined.

Case 3. Figure 4 (A and B) illustrates scans of a 46

FIG. 4, A

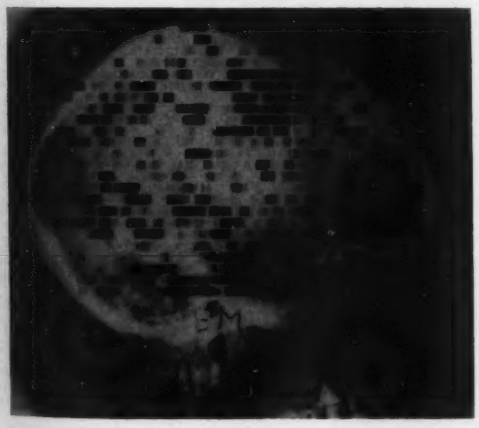
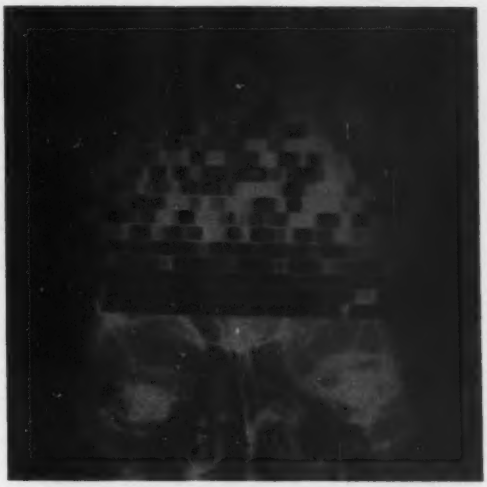


FIG. 4, B



year old white, right-handed woman who was admitted to the hospital with a chief complaint of seizures. The patient had her first seizure in 1949. She had a premonitory aura of a strange feeling in either the right or left side of the head followed by blurring of vision. Following this the left hand would elevate and her head would turn to the left and she became unconscious. These episodes occurred frequently at night. Anticonvulsant medication gave a good measure of control of these episodes, but she continued to have about one per month. X-ray films of the skull taken prior to admission revealed a calcified mass in the right fronto-parietal region. The general physical examination showed evidence of a left radical mastectomy performed in 1951 and a right simple mastectomy in 1952. The former was done for carcinoma, the latter for cystic disease. The remainder of the general physical examination was not remarkable. The neurologic examination failed to reveal any abnormality.

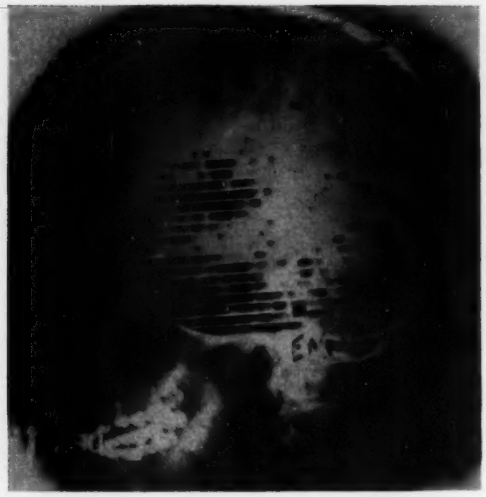
A previous arteriogram was reviewed and a mass lesion was evident. The scan revealed specific abnormal activity in the parasagittal area of the posterior frontal lobe on the right side. It is well visualized in both the right lateral and frontal projections.

Operation subsequently verified the presence of a meningioma.

Case 4. Figure 5 (A and B) shows scans of an 11 year old white, right-handed girl who was admitted to the hospital with the chief complaint of progressive unsteadiness. The patient was asymptomatic until 11 months prior to admission at which time she had a seizure involving the right arm and left hip. In subsequent months she had frequent staggering episodes in which she had no control of the right lower extremity and often fell. For several weeks prior to admission she had episodes in which the entire body seemed to shake. Speech and vision were apparently spared.

On admission to the hospital the general physical examination was not remarkable. The neurologic examination revealed that her handwriting was quite

FIG. 5, A



tremulous. There was a slight tremor when the hands were extended, and the gait was markedly unsteady. There was bilateral papilledema with slightly enlarged blind spots. There was marked ataxia on the finger-to-nose test as well as the heel-to-shin test. The Romberg was consistently positive to the right. No sensory abnormalities were noted.

X-ray examination of the skull revealed it to be somewhat enlarged and there was thinning of the posterior clinoids. Digital impressions were also present. A ventriculogram revealed an obstructive hydrocephalus with a filling defect in the anterior third ventricle. An exploration of the posterior fossa was performed which was negative for tumor, and this was followed by a Torkildsen procedure.

FIG. 5, B

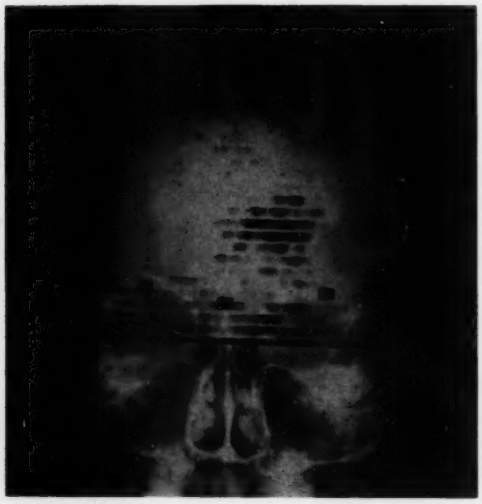


FIG. 6, A

The left lateral scan shows circumferential area of increased specific abnormal activity immediately above the temporal muscle. The frontal scan reveals this to be a deep-seated lesion, midline in location with extension to the left. No pathologic verification is available in this case.

Case 5. Figure 6 (A and B) represents scans of a 51 year old white, right-handed man who was admitted to the hospital with the chief complaint of neck pain of one year's duration. The pain began in the occipital area with a radiation up and down the left side of the neck. It was aggravated by throwing the head backward and to the left. The patient also complained of a "blacking out" of vision in the left eye when this occurred. There was no history of vertigo, but occasional tinnitus bilaterally was noted. There was a question of hearing impairment but nothing definite.

The general physical examination was not remarkable. The pertinent neurologic findings included a unilateral papilledema of 4 to 5 diopters in the right eye and a nerve type loss on the right with no caloric

FIG. 6, B

FIG. 7, A

response on the right. The remainder of the neurologic examination was not remarkable.

X-ray examination of the skull failed to reveal enlargement of the porus acusticus. A right carotid arteriogram was negative. A ventriculogram revealed marked dilatation of the lateral and third ventricle. The upper part of the aqueduct of Sylvius appeared to be pushed upward, and no air was seen in the posterior fossa. The right lateral scan revealed specific abnormal activity which gave the impression that there was extension of the mass from the posterior fossa into the middle fossa. The occipital scan shows a normal specific activity in the cervical muscles with an increase on the right side.

At operation this impression was confirmed, and a large acoustic neurinoma with supratentorial extension was removed.

Case 6. Figure 7 (A and B) illustrates scans of a 64

FIG. 7, B

year old, right-handed Puerto Rican who was admitted to the hospital for investigation of a progressive aphasia. One month prior to admission the patient developed garbled speech and was unable to express himself. A lumbar puncture performed in Puerto Rico revealed a cerebrospinal fluid protein of 156 mg. per 100 cc.

X-ray films of the skull were considered normal. An electroencephalogram showed absence of the faster frequencies throughout the left hemisphere with abnormal delta activity localized to the anterior portion of the left temporal lobe. A left cerebral arteriogram revealed a space occupying lesion of the left temporal lobe. The scan revealed abnormal specific activity as seen in the frontal and lateral projections. A large area of specific abnormal activity is seen in the left lateral projection encompassing the posterior temporoparietal area. The frontal projection reveals this to be a deep-seated lesion which extends laterally to the surface, and almost to the midline medially.

Because of the involvement of the dominant hemisphere only a needle biopsy of the mass was performed. This failed to demonstrate a tumor. X-ray therapy was instituted.

Summary

The localization of brain tumors by means of the focusing collimator and scintillation counter with photoscan attachment has been graphically presented. Improved instrumentation has resulted in scans of such quality that they may easily be interpreted. This ancillary diagnostic tool is as useful as air studies or arteriography, and it carries none of the mortality or morbidity of either.

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A Surgeon Views Radioactive Iodine and the Thyroid Problem*

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A REVIEW of the impact of radioactive iodine on the diagnosis and treatment of diseases of the thyroid involves a look at I^{131} and the thyroid from the following aspects:

1. In diagnostic tracer doses
2. For "scanning"
3. In the treatment of toxic diffuse goiter
4. In the treatment of toxic nodular goiter
5. In the treatment of cancer of the thyroid.

I^{131} in Diagnosis

Numerous comparative studies of the value of the various diagnostic tests for disturbance of thyroid function show that all of them give reasonably accurate results, that no one of them is definitely superior to the others, and that, above all, none of them singly or in combination is superior to the clinical history and examination.[1-9] In 80 to 90% of patients with hyperthyroidism the physician will make the diagnosis with certainty on the clinical findings alone, and the laboratory findings merely confirm his opinion. In only about 10% of cases is there any real diagnostic problem. If there is a problem the three laboratory tests in common use, the basal metabolic rate (B.M.R.), the chemical protein-bound iodine (PBI.), and the 24 hour uptake of I^{131} are of considerable help. It may be that a B.M.R., carefully determined under ideal circumstances, is still the most accurate way of assessing thyroid function. It has the distinct advantages in that it is not disturbed by medication, and it does indicate the severity of the thyroid dysfunction. It can also be said that a PBI. obtained by careful chemical technic is quite diagnostic, but it does require unusual technical competence, and is voided by iodine medication. The 24 hour uptake of I^{131} is not always reliable, but it has some advantages as well as disadvantages. There are four disadvantages in evaluating the results of uptake tests: (1) the patient has been taking iodine; (2) the test is not reliable in the group of patients with hyperthyroidism due to toxic nodular goiter; (3) it is erratic in determining thyroid deficiency; and (4) in cases of toxic diffuse goiter, where it is usually dependable, it does not indicate the degree and there is some overlapping between the euthyroid and the hyperthyroid states. On the other hand if there is a real diagnostic problem, it will usually be in a patient without thyroid enlargement in whom hyperthyroidism, if any, will be due to a diffusely hyperplastic gland which will nearly always give a high uptake value even if the disease is of mild degree. The fact that the uptake study does not indicate the degree of hyperthyroidism, but is to a certain extent an "all-or-none" reaction, is of advantage from a purely diagnostic point of view, but is useless of course if one is trying to estimate the severity of the disease. If the equipment is available, the tracer test is inexpensive and is subject to few unrecognizable technical errors, either on the part of the patient or the technician. If the equipment is purchased for the sole purpose of thyroid diagnosis, it is doubtful that the expense will justify the re-

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turn as measured by an improvement in diagnostic accuracy based on a combination of clinical judgment and the B.M.R.

Many successful diagnostic tests based upon the metabolic circuit of iodine have been devised using I^{131}. The most important are as follows:

1. The 24 hour uptake
2. One to six hour uptakes
3. Urinary excretion
4. PBI-131 and conversion ratios
5. Clearance rates
6. Suppressive effect of thyroid and I-2
7. *In vitro* red cell uptake.

The 24 hour thyroid uptake of radioactive iodine is the most generally used determination and suffices for routine clinical purposes. There is one disadvantage in all of the other tests in that if the patient is to be given a therapeutic dose, it is mandatory to know the maximum uptake which is always reached in hyperthyroid patients within 24 hours. Thus, if therapy is contemplated, a 24 hour uptake (or at least a 12 hour uptake) is necessary in practically all cases. Of the other tracer tests mentioned, none increase clinical accuracy to such an extent as to warrant their adoption in the ordinary laboratory. It is true that a battery of tests will better the statistical accuracy somewhat, but the betterment is unlikely to be worth the trouble and expense to obtain it. Neither hyperthyroidism or hypothyroidism is such an obscure clinical entity as to require an expensive and complicated thyroid profile, or an outline of all the "parameters of thyroid function."

Scanning. Ingenious electronic and mechanical apparatus has been devised to map out the topographical deposition of I^{131} in thyroid tissue. The scan will outline the borders of a functioning thyroid gland fairly well, it will show nonfunctioning areas only if they are 2 cm. or more in diameter. It will depict functioning thyroid tissue elsewhere than in the neck, but will not outline extra-thyroidal thyroid tissue in the neck unless the thyroid gland has been ablated. The procedure requires about 20 minutes and is not expensive, providing one owns the equipment. This costs from $3,000 to $6,000. Is the information to be gained worth the cost of the equipment? The "scan" may be used for the following purposes:

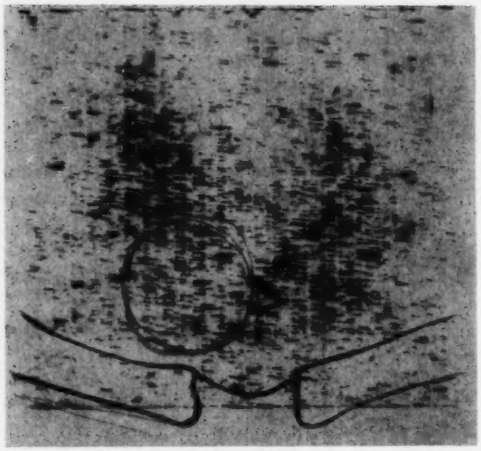
1. To establish the size of an exophthalmic goiter
2. To determine whether a nodule is "hot" or "cold"
3. To localize intrathoracic, aberrant, or metastatic goiter.

1. One can clearly outline the borders of a toxic diffuse goiter and use this information in a formula to calculate the weight of the gland, to aid in turn in calculating the size of a therapeutic dose of I^{131}.[10,11] It is reasonable to suppose that this is a better method of calculating weight than is palpation, but unfortunately weight is only one factor, and may not be the important factor in determining dosage. The effective half-life is equally important and can perhaps be estimated with reasonable accuracy. The degree of radiosensitivity of any particular gland is also an important factor, but it cannot be estimated. I believe it is reasonable to state that the silhouette of the thyroid gland as obtained by scanning may be helpful but is not essential in estimating the therapeutic dose.

2. Is the nodule "hot" or "cold"? One might also properly ask if the nodule is "hot" or "cold," so what? It must be remembered that a nonfunctioning nodule must reach the size of a sphere 2 cm. in diameter before resolution is sufficient to separate it from the surrounding normal thyroid. A scan, then, is usually applicable only to lumps over 2 cm. in diameter. If a nodule does not accumulate radioactive iodine, it may or may not be malignant (Fig. 1). If a nodule shows definite evidence of a normal or increased avidity for iodine, it is obviously very unlikely to be malignant (Fig. 1). I would estimate that only about 15% of nodules in euthyroid patients pick up I^{131} freely. The remainder do not. One would be reassured in respect to these 15% of cases but in the remaining 85% the probability of malignancy would remain at about the same percentage relationship as before the scan. There is one advantage, however, in that if one finds a nodule with a marked avidity for iodine, it may disappear on thyroid therapy (Fig. 2).

3. The scan is not too successful in localizing aberrant or metastatic goiter. Not infrequently the clinician requests a scan because of an intrathoracic tumor with the idea that if it is goiter it will pick up I^{131}. Unfortunately the problem is not solved so simply

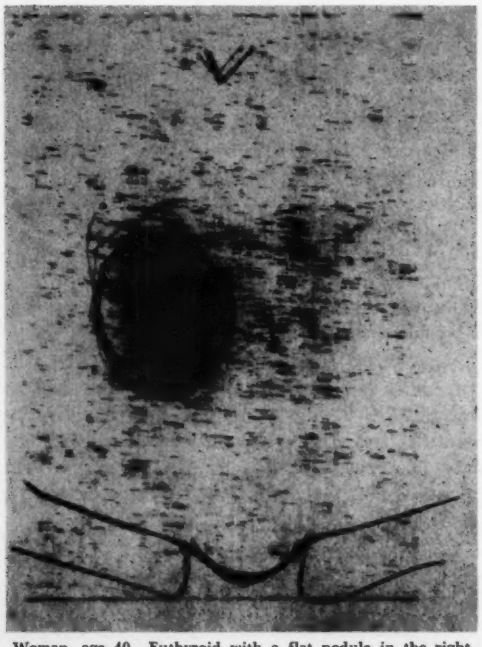
FIG. 1



Male patient, age 33, with a clinical solitary nodule in the right lower pole. There is diminished uptake in the region of the nodule and the upper portion of the right lobe seems squeezed in an upward direction. At operation it was found that he had 3 benign nodules conglomerated in the lower half of the gland.

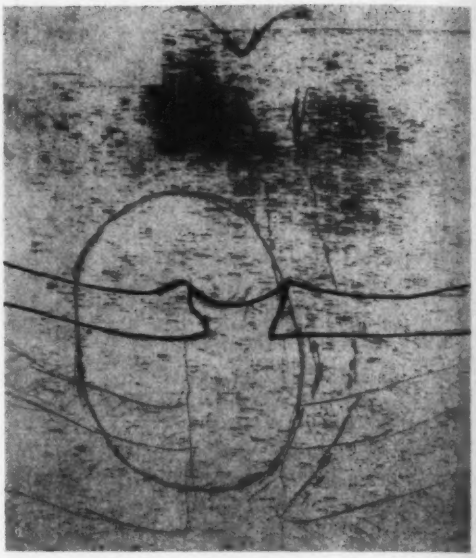
since most nodular goiters and most intrathoracic goiters do not accumulate I^{131}. The failure of a mass to register iodine uptake by

FIG. 2



Woman, age 40. Euthyroid with a flat nodule in the right lobe. At 24 hours she had a 30% uptake, practically all of it in the nodule. The mass diminished in size on thyroid therapy.

FIG. 3



Man, age 51. Large intrathoracic goiter found on x-ray. There is no uptake by the nodule which proved to be benign. There is some compression of the right lobe which is pushed upward. The distortion must be interpreted by the physical findings.

no means rules out the possibility that it is a goiter. Frequently, however, there is some distortion of the thyroid pattern in the neck in the presence of an intrathoracic goiter, in fact it would be unusual indeed for a patient with an intrathoracic goiter to show two normal, symmetrical lobes on a thyroid scan (Fig. 3).

Treatment

Toxic Diffuse Goiter.

Therapy with radioiodine (I^{131}) in hyperthyroidism is primarily indicated in exophthalmic or toxic diffuse goiter rather than in toxic nodular goiter. The only major objection to the use of I^{131} is the possibility that it is a carcinogen. There is evidence indicating that irradiation of the region of the neck in infants predisposes to cancer of the thyroid. The best evidence has been presented by Simpson and Hempelmann[12] who traced 1,502 infants who had been treated by x-ray for thymic enlargement. Of these, 11 developed thyroid cancer, while there was none in 1,933 untreated siblings. There has been one report of significance by Sheline, Lindsay and Bell[13] of the occurrence of thyroid nodules in children following therapy with radioiodine for

hyperthyroidism. Five to ten years following therapy, thyroid nodules appeared in 3 of the 18 patients less than 20 years old. Two of these children with late nodules were among the 5 treated before the age of 10 years. One showed invasion through its capsule and was classified as an invasive adenoma, a low-grade carcinoma. For the above reasons, children should not be treated with radioiodine. Another contraindication, of course, is pregnancy.

Because of the theoretical danger of cancer, I^{131} therapy at first was selective, chiefly for poor-risk patients past 40 to 50 years of age, and for postoperative recurrent exophthalmic goiter. As no tumors were observed to occur, the threshold was gradually lowered to include virtually all patients with exophthalmic goiter over 40 years of age, and as each year passes by without evidence of carcinogenic effect, the limit is lowered by a year and sometimes more. At present it would seem unlikely that the hypothetical danger of a future incurable cancer would equal the 0.3 to 1.0% mortality rate of a thyroidectomy for toxic diffuse goiter. The situation as regards I^{131} and cancer can be summarized succinctly and rather poignantly by a poem which had its origin a number of years ago in that great center of erudition, Harvard!

There is a little man who isn't there,
A-sitting on the stair;
There he sits day after day,
Oh, how I wish he would go away.

The indications for I^{131} in the treatment of toxic diffuse goiter are as follows:

1. In postoperative recurrence
2. In patients over the age of 40
3. In patients sensitive to iodine
4. Excessive risk of operation
5. Preferably small goiters.

Most physicians will agree that a postoperative recurrence is an indication for radioactive iodine. The age of 40 is taken as the dividing line between surgery and radioiodine, but as indicated above, the line undulates somewhat up and down, so it might best be described as age 40 plus, or minus 20. The occasional patient sensitive to iodine premedication should be given I^{131}. If a patient is quite toxic and is sensitive to propylthiouracil, he also should receive I^{131}. I see no reason why a surgeon should accept a high-risk thyroidectomy when he can accomplish the same thing by a drink of water. A patient with a small goiter requires a smaller dose of radioiodine than one with a large goiter, and the result is more satisfactory. There is a tendency, then, to administer I^{131} to patients with no enlargement of the thyroid gland, and to do a thyroidectomy on those with large goiters.

There are some disadvantages and some precautions to be taken in using radioactive iodine. There is an occasional patient who has had iodine deposited within his body, usually lipiodol, who will not accumulate radioactive iodine. Once in a while, for some unknown reason, an exophthalmic goiter does not respond to I^{131}. If a patient is very toxic, some doubt may arise in the advisability of administering I^{131} without preparation by one of the antithyroid drugs. Fortunately, the patient with exophthalmic goiter tolerates I^{131} therapy very well, post-therapy reactions are not severe, but they do occur and can be fatal. A large weight loss, profound weakness, or excessive nervousness is indication for a few weeks preparation with propylthiouracil or methimazole (Tapazole). But the most important objection to I^{131} is a high incidence of hypothyroidism. There is a distinct tendency for patients to become hypothyroid following I^{131} therapy, early and late, but there is little tendency for recurrence. On the other hand, following operation there is less tendency to myxedema, but a much greater tendency to recurrence.

Toxic Nodular Goiter.

In toxic nodular goiter, thyroidectomy is still the preferred form of treatment. This operation is uniformly satisfactory; it removes the nodules, and is followed by a low incidence of recurrence. In nodular goiter, therapy requires large doses of I^{131} and frequently several large doses. It is well to remember, however, that I^{131} therapy may be effective in toxic nodular goiters, and it may be used in the preoperative treatment, or even as definitive treatment when the operative risk is high. This may frequently be the situation in patients over 70 years of age with severe cardiac impairment. If operation is contemplated on such a patient, the preoperative treatment will require several months. In such a circumstance one could administer a large therapeutic dose of radioactive iodine, followed by antithyroid therapy, and thus obtain a greater degree of improvement without incurring any

loss of time. The therapeutic result of I^{131} in toxic nodular goiter depends on the percentage of thyroid uptake and the size of the goiter.

Heretofore, one of the difficulties in treating toxic nodular goiter has been the rather low uptake as compared to the size of the goiter. This difficulty can often be overcome by the use of thyroid-stimulating hormone (TSH.). If the thyroid accumulates less than 40% of the tracer dose, the uptake should be enhanced with TSH. Five units of TSH. (Thytropar, The Armour Laboratories) are given intramuscularly, 24 hours later the tracer dose is administered, and assayed in the neck on the following day. If there is a substantial increase in uptake, a second 5 units is injected, and the therapeutic dose given 24 hours later. Using TSH. in this manner, we have been able to treat effectively a number of toxic nodular goiters. For this purpose we use much larger doses than is customary, not hesitating to give 40 or 50 millicuries at a time. These doses are followed by an occasional sharp reaction, but some risk must be accepted if anything is to be accomplished. If a large nodular goiter accumulates less than 20% of the tracer dose, and the uptake cannot be increased by TSH., it is better to prepare the poor risk patient with antithyroid drugs and arrange for a thyroidectomy, regardless of risk.

Cancer.

Of all the patients with cancer of the thyroid, less than 10% are treatable with I^{131}. The basic indication for I^{131} therapy is a tumor which cannot be removed surgically, but which can pick up, or can be induced to pick up I^{131}.

Therapy with I^{131} is of no value as a prophylactic measure. The destruction by internal irradiation is produced by beta rays with a maximum effective range of only 2 mm. The cross-fire effect of each discrete center of radiation deposited within a small tumor diminishes as the tumor diminishes in size, so that more accumulation is necessary in a tumor 1 mm. in diameter than in one 3 mm. in diameter. At cellular size it would be impossible for a tumor to collect sufficient I^{131} to destroy itself. Even if a large mass of normal thyroid receives a destructive dose, frequently the outer 1 or 2 mm. will survive because of lessened cross-fire effect. From this consideration alone, the question arises whether it is possible at any time to destroy completely all thyroid tissue, especially if its I^{131} uptake is as low as it is in cancer of the thyroid.

One can rule out for treatment with I^{131} all patients in whom the tumor has been removed surgically, and who have no clinical evidence of recurrence or metastases, and all patients who have histologically proved true papillary carcinomas or undifferentiated carcinoma. However, there is so much overlap between follicular tumors which may be amenable to treatment and the relatively benign papillary tumors on the one side, and the more malignant, undifferentiated tumors on the other side, that one should not rely on the histologic appearance of a single microscopic section. In other words, one may rule out all patients with any type of malignancy in which there is no evidence anywhere of follicle formation. After these categories of patients have been eliminated, there will be left on more than 20% of patients for whom investigation with the use of I^{131} will be warranted, and of these about half will be found acceptable for treatment with I^{131}. Unfortunately, according to these figures, no more than one patient in 20 with carcinoma of the thyroid will receive any benefit from internal radiotherapy.

The results of I^{131} therapy in cancer of the thyroid are disappointing. I have had one moribund patient with a paraplegia due to a metastatic carcinoma of the lumbar spine who had an astonishing result. He regained the use of his legs, returned to work, and died 6 years later of a coronary insufficiency. Three others obtained some palliation. This is all. The very best analysis of the problem has been recorded by Sheline and Miller.[14] They had, in all, 124 patients with carcinoma of the thyroid, 86 were investigated for treatment with I^{131}, 23 were selected for treatment, 18 completed treatment, and 11 showed arrest or regression of the disease.

Summary

1. The tracer dose of radioactive iodine is helpful in diagnosis but is not a necessity.

2. The scan will determine if nodules are "hot" or "cold," but since benign nodules are usually "cold," it does not constitute a good

means of distinguishing benign from malignant nodules. It will occasionally pick up a "hot" nodule that does not need to be operated on. Its use in determining the size of an exophthalmic goiter is problematical.

3. I^{131} is a better form of therapy than surgery in exophthalmic goiter in adult patients.

4. I^{131} can be used as preoperative and even definitive treatment in elderly patients with toxic nodular goiter in whom the surgical mortality is excessive.

5. I^{131} therapy in cancer of the thyroid is disappointing, but since an occasional patient does respond to such treatment it should be considered in each case.

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What Every Doctor Should Know About "Fallout"*

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IN THE ANCIENT HISTORY of warfare the impact on the civilian populace was frequently profound. Aside from civil disruption and slaughter, the vanquished nation found itself subjected to severe taxation or to slavery as the accepted spoils of war.

In middle history, the civil population was affected more by the economic strains, as the rules of war restricted the combat more rigidly to the fighting elements. The siege of cities with its consequent horrors to the citizens was replaced by more efficient weapons so that combatants were required to devote their energies to the destruction of fighting potential.

The circle has now been closed with the development of methods of destroying large areas and its consequent overflow onto civilians adjacent to military targets. With the advent of thermonuclear weapons, a war using such devices presents the problem of coverage of large areas by radioactive fallout and its attendant threat to the lives or health of people in extensive areas scores to hundreds of miles from the detonation. Nonetheless, management of this problem presents significant possibilities of hope and survival.

National survival and survival of the population are synonymous. Therefore, dissemination to the public of information on how to stay alive is of vital import. Our national policy of deterrence of aggression by threat of retaliation has thus far been successful. An aggressor must certainly hesitate to launch a thermonuclear attack so long as he rests as-

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sured in the knowledge that his own country would be destroyed in return.

As this point of potential mutual national suicide is reached, another significant element of the strategy of deterrence comes into play. A country that can absorb an initial attack, retaliate in kind, and maintain the potential for continued survival and for continued prosecution of the war is a much less tempting target to an aggressor. The will to continue the resistance must have its roots in the faith and belief of the people of the nation that they most certainly can survive the initial attack through practical methods, and that they can rebuild their country in a reasonable time.

Although the destruction of target areas is terrifying to contemplate, a much greater geographic area can be covered by radioactive fallout. With a minimum of technical information, with careful planning and very modest expenditures, conservation of a significant percentage of our most valuable resource—our people—becomes possible. The saving of lives both by preventive measures and by education is an accepted role of the medical practitioner. Therefore, his assistance is logical in certain aspects of public indoctrination in survival in fallout.

A quick review of the mode of formation of radioactive fallout is in order. Fortunately, this morning, we have had the advantage of Lt. Mitchell's lucid introduction to basic nuclear physics. The information he and the staff from Bethesda so ably presented applies to the radioactive atoms in fallout material precisely as it does to the radioactive atoms used in clinical diagnostic, therapeutic and tracer procedures.

In a nuclear weapon, just as in a nuclear reactor, the large atoms of the isotopes of uranium or plutonium are split or fissioned by bombarding neutrons. The physical reaction is identical. The fragments are not in optimum energy balance and to reach a baseline of stability give up energy by throwing out particles and electromagnetic radiation. These for the most part are beta particles and gamma rays. Each fragment then is truly a radioactive isotope and a large variety are present in this mixture.

In a nuclear reactor the rate at which these fissioning events take place is controlled and held at a constant level. In a bomb, on the other hand, the rate of fissioning is deliberately increased to yield as much of the energy released by the fission process as possible in the shortest time. This, of course, produces the blast—the basic reason for the bomb.

If such a weapon is detonated so the fireball touches the surface of the earth, any material in the immediate vicinity of the fireball is vaporized by the tremendous heat and carried upwards into the atmosphere. As it expands, cools and condenses, this material traps the radioactive isotopes and, governed by gravity, particle size, the winds and the climate carries the radioactive material down to earth over a large area. Herein lies our problem.

By reflecting back to our knowledge of radioactive decay we realize that each isotope emits its energy at a different and specific rate. Therefore, the radiation rate from a mixture of many isotopes made up of many half-lives, from very short to very long ones, will be much more intense at first and die down rapidly at the beginning as the most short-lived radioactive atoms achieve stability. This one piece of information—that the radiation intensity is very high at first and dies down quickly—is vital to our survival. The most urgent need for protection is during the first few hours after arrival of the fallout material.

The problems of management of ionizing radiations as applied to the patient are certainly not strangers to the medical profession. For many years we have been aware of the dangers of too much radium deposited in bone from the chronic ingestion of radium salts. We have not only been aware of, but have judiciously used the ionizing properties of x-rays for the control of disease, both malignant and benign. This Symposium is devoted to a better understanding of the application of radioactive isotopes placed inside the body for improved diagnosis and therapy.

In the laboratory and clinic we reduce unnecessary exposures in three ways: we keep the exposure time as short as possible; we keep the working staff as far from the source as reason and the procedures will allow; and, we interpose dense materials as an absorbing barrier to protect the body against undesired exposures. The working philosophy is simply that of providing a localized, controlled area in which the radiations may be used.

In an area of generalized, uncontrolled

radiation such as the fallout field, the philosophy is simply reversed. Instead of controlling the area in which the hazard exists, we must provide a controlled area in which there is safety and protection. This area in essence is a fallout shelter. The three fundamental technics of protection do not change at all. First, time of exposure must be held to a minimum. Second, distance from the source should be increased as far as possible. Third, shielding by a large mass of material must be interposed between the radiation source and the body.

With this basic knowledge, how can we apply it in a practical way to the requirements of our profession under such disastrous conditions as thermonuclear war? It is vital for us to recognize the magnitude of the problem facing our nation after such an attack. Aside from casualties of war the disease processes of peacetime continue inexorably. In the social disruption after such an attack the problems of public sanitation, proper control of food sources to ensure wholesome food supplies, the protection and testing of water supply and the management of epidemic disease must be faced. Survival depends on proper control of these factors and we all recognize in them certain medical responsibilities.

The demands on the medical profession to support national survival are very great. The time required to educate a physician is such that under this situation he becomes a resource to the country of unusual value. The nation cannot afford to lose his services as a casualty to radiation sickness. However, by adequate prior planning on the part of the medical profession in coordination with local governmental and civil defense authorities, good medical care can be made available to the people for whose health we are responsible.

By careful planning the dispersal of doctors through the community in well sheltered sites can be accomplished. Thus, the patient may be brought to the physician in an emergency and receive only one acceptable exposure to the radiation. If the doctor were required to go from patient to patient, he obviously would be subjected to repeated and cumulative doses of radiation.

I must emphasize that we are discussing that vast area outside the immediate area of blast and heat damage. Protection from these effects is quite a different proposition from fallout shielding. The fallout area would not produce traumatic and thermal casualties. The medical care problem is that of the usual peacetime medical and surgical diseases. The principal factor is control of the operational aspects of medical care, including transportation, supplies and communications, to avoid unacceptable radiation exposure both to the doctor and the patient.

In summary, the most important features of radioactive fallout which we need to comprehend are the decay rate allowing high dose rates early with a rapid falloff during the first few hours. The second concept of importance is the understanding of shielding —the fact that solid materials in sufficient quantity will absorb the ionizing radiations and protect persons from their undesirable effects.

Technical assistance in developing our plans for medical support can be obtained from physicists, engineers and architects. There are now available numerous publications from the Office of Civil and Defense Mobilization as well as several currently being written which give reliable detailed information. It is our firm belief that a demonstrated intention and capability to survive a thermonuclear war will serve as an important deterrent to the war we hope will never come.

The Management of Victims of Radiation Accident*

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SINCE THE FIRST FISSION of the uranium atom was accomplished about twenty years ago, there has been a continuous increase in the amount of radioactive materials produced in this country. Part of this material has occurred in the assembly and stockpiling of nuclear weapons. Another large amount has been employed in peacetime pursuits such as in the production of research, training and power reactors, and in basic sciences and medicine. The fuel used in atomic weapons and in reactors has offered a greater potentiality in regards to producing radioactivity since each atom of the fuel undergoing fission breaks into two atoms of radioactive material having more energetic emissions than the mother, or fuel substance.

Power reactors have become more prevalent each year. It has been stated that 370 reactors are under construction or planned in the Nuclear Power Reactor Program.[1] In addition, the armed forces have several nuclear powered ships afloat and have many more planned. The land based power reactors have been placed throughout the country and the nuclear power ships will visit our major ports. While the safety factors in all power reactors are very specific and nearly foolproof, it is realized that an accident could occur with any arrangement of such potentiality.

If such an accident would occur in a 500,000 kw. reactor after 180 days of operation and 24 hours of cooling, the radioactive materials shown in table 1 would be present.[2]

If a complete excursion in a reactor of the above size were to occur which, as has been stated is extremely unlikely, the tremendous radioactivity would exist in the capsule housing the reactor fuel. It is also unlikely that any would escape, but if the container ruptured, one would not expect more than 50% to escape.[2] However, even this would be a tremendous amount of radioactive material that could be spread over the countryside surrounding the above reactor.

TABLE 1

Total fission products	4.1×10^8 curies
Strontium-90	3×10^6 curies
Strontium-89	1.7×10^7 curies
Cerium	8×10^6 curies
Plutonium-239	3.8×10^3 curies
Iodines	5×10^7 curies
Noble gases	3.4×10^7 curies
Total volatile fission products	8.4×10^7 curies

Basic sciences and industry are also using radioisotopes in many ways, particularly in gauging measurements, and as a source of energy for industrial radiography. Here again, the large number of such sources that are being used adds to the potentiality of accidents of a peacetime nature.

The medical profession was one of the first to accept the use of artificially produced radioisotopes in the diagnosis and treatment of disease. This use includes teletherapy units which are used as a substitute for deep x-ray therapy in the treatment of cancer. There are over 400 such units present in this country, and although it is unlikely the radioactivity contained in these units will leak, this has happened to a negligible degree.

These uses are continually increasing in number as well as in size of the radioactive sources. Thus, the danger of accidents or incidents are consequently increasing. It behooves the medical profession to make definite plans to cope with such accidents or incidents.

Possible Types of Accidents

Power Reactors.

If any type of reactor were to undergo an accident, this accident usually would be of one of two types. Either the reactor would become supercritical and undergo an excursion,

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The opinions expressed herein are those of the author and not necessarily those of the Department of the Navy.

or, by some manner or other, the coolant would be drained from the reactor which, in effect, would result in a supercritical condition.[2] In either case, the tremendous amount of heat that would be instantaneously formed in the fuel core would cause a melting of the fuel and a possible rupture of the container. If the latter happened, it would allow radioactive fission products, about 20% of which are volatile,[2] as well as some of the fuel substance, to escape from the container into the surrounding area. If the reactor were air-cooled, some of this material might be blown from the reactor into the surrounding atmosphere. If the reactor were water-cooled, the radioactive materials might be spread by the cooling water to natural bodies of water.

At the time of the reactor excursion, a large amount of gamma and neutron radiation would be emitted. Much of this would be absorbed by the shielding of the reactor. However, people in the immediate vicinity would probably receive an appreciable dose of combined gamma and neutron radiation which, in certain instances, may be fatal. If the fuel container ruptured, this would add external and internal contamination by radioactive materials to this same group of people.

Industrial Sources.

Most sources of radiation used in industry are of gamma emitters, such as cobalt-60 or iridium-192. These are used to measure thickness and density of construction materials as well as to take films showing defects in bearings, shafts, etc. Many beta emitting isotopes are also used as a gauge of thickness of thin material. The use of the gamma emitting isotopes increases the possibility that surrounding personnel may be exposed to large doses of external radiation. And again, the container of the radioactive source may become ruptured allowing a spreading of the radioactive material through the surrounding area with resultant external and internal contamination.

Nuclear Weapons.

It is almost impossible to visualize an accidental explosion from a nuclear weapon.[3] However, there is always a danger that during the transporting of nuclear weapons from one site to another, either by vehicle or aircraft, the nuclear fuel component may leak from the container. This is especially true in the case of an aircraft accident involving a nuclear weapon. In such a case the nuclear material may be scattered over an area at the site of the crash and the crew of the aircraft or the vehicle as well as people living in the immediate vicinity may be contaminated by this radioactive material. Thus, the problem would be mainly of external and internal contamination depending upon whether the radioactive material entered the bodies of those exposed.

Medical Sources of Radiation.

Many of the overexposures in the past, particularly in the early days of the use of radium and x-rays, were brought about by the injudicious use and handling of sources of medical radiation. These types of accidents and overexposures have been eliminated. With the increasing use of radioisotopes in medicine, either in diagnosis or in therapy, there is a new possibility that an accident or incident of overexposure might occur, but because the medical team using this form of radioactivity is trained in monitoring and handling of the materials, the chances of serious accidents from medical sources are minimal.

Methods of Exposure.

The complexity of these problems may be illustrated by table 2.

Personnel who have been exposed to nuclear accidents may have been exposed to the above types of radiation singly, or in any combination. Ordinarily, the management of the patient would depend upon the type of radiation exposure as well as the total dose of radiation received. However, a medical center which has the capabilities for the care and management of radiation casualties will have many personnel referred to them who have been involved in radiation incidents, without actual exposure to doses in the range of the Maximum Permissible Dose of ionizing radiation. Thus, the wheat must be seeded from the chaff and no doubt there will be many more possible exposures to evaluate than actual exposures.

TABLE 2

1. (External) electromagnetic radiation (gamma, x-ray).
2. (External) charged particular radiation (beta, proton, alpha).
3. (External) noncharged particular radiation (neutron).
4. Internal emitters (Pu^{239}, Ra^{226}, Th^{230}, Ca^{137}, Sr^{90}, H^3, etc.).

Patients in the immediate vicinity of a reactor accident would possibly receive all four types of radiation listed in table 2. Patients in the vicinity of an accident involving a nuclear weapon would probably receive the types of radiation listed in 2. and 4. of table 2. Patients exposed to a spill of a source of radioactivity, used either in industry or medicine, would be exposed to the types of radiation listed in 1., 2., or 4. of the table, depending upon the type of source of radioactivity involved in the accident.

Requirements for Dosimetry

During this discussion, the subject of the LD-50 dose or *lethal dose* of radiation to the human will be avoided insofar as numbers are concerned. This is for the obviously good reason that the question of LD-50 in the human being is at present in a state of flux. For many years the reports published concerning this figure used 450 r. in air as the approximate exposure dose of the LD-50 to the human being. This was based upon animal studies and extrapolation of this animal data to the human being. This also has been quite obviously in error to the effect that expected symptoms resulting from this use of extrapolation measurements have not proven valid in humans. Experience within the past two years, in total body radiation therapy in the human being, has shown that the human, at least in cases of hospitalized patients, can withstand a higher dose than 450 r. without suffering the effects prescribed from extrapolated animal data. Also, the minimum lethal dose of the human being is not actually known at the present time. For this reason, during the course of this discussion, we will studiously avoid stating any prescribed doses. It should be mentioned that for the human two different LD-50 doses should be considered. One dose would be the LD-50 for the hospital patient who is receiving meticulous nursing care and the best in management. This would be higher than the LD-50 dose for the casualty in the field of military action, or during a large scale nuclear catastrophe, either peacetime or wartime.[4]

As has been stated, the management of the case depends upon the type of radiation to which the patient was exposed. For instance, if the patient suffered a large dose of an industrial source of cobalt-60 radiation, his exposure would be to pure gamma rays, an external type of exposure which is listed in 1. of table 2.

As a general rule it is not too difficult to determine the type of exposure to which the patient has been exposed. However, to attempt to determine a dose of radiation to which he was exposed (measured in r.) or, more important, the absorbed dose of radiation the patient received (measured in rad) is an extremely difficult matter. Most dosage determinations are made by various electronic devices which measure the ionization of air or a gas. In addition, some doses are measured by the use of film badges in which films with different speed emulsions can be used to measure the exposed dose of radiation. Neither of these types is satisfactory during an accident primarily because the personnel dosimeters, if worn by people exposed to routine radiation, cannot register a high dose of radiation and are usually off scale if a serious accident occurs. Usually reconstruction of the accident is required to attempt an estimate of the dose the patient has received.

Perhaps the most practical method of determining the dose of radiation that a patient received in the course of a peacetime nuclear accident is by the clinical response. The patient's course must be followed for a matter of several days to weeks before he reacts in a manner that can be evaluated clinically to his assault from ionizing radiation. Meanwhile, it may be necessary to treat the patient either from a supportive standpoint or from a definitive standpoint. Thus, by the time the clinical response of the patient has reached a stage by which a dose estimate may be made, the patient may have acquired treatment that, in certain instances, might be unnecessary.

At the present time the most dependable method of following the course of a patient and attempting to adjudge the radiation dosage he might have received is by his peripheral blood count. In the past it has been understood that following a large dose of acute radiation in the near lethal or lethal range, the fall in the white count, and the platelet count will probably not reach its lower ebb for 4 to 6 weeks.[5] Recent information leads us to believe that this is not true. More likely, the fall in the white blood cells as well as the platelet elements will become more rapid as the dose increases. Whether or not there is a

linear response to the dose in depression of the white blood elements and the platelets is not yet understood, although this may be so.

Another determination that has been made on patients receiving total body radiation is the urine measurement of an abnormal amino acid, Baiba (beta-aminoisobutyric acid). This can be done by various methods such as chromatography, ion exchange, etc. The urine levels of serine and taurine also appear to increase following exposure to large doses of radiation. The urinary uric acid level increases. There is relatively little or no change in the blood chemical constituents, particularly in the electrolytes.[4] Special enzymatic studies are now underway to determine whether or not there are significant changes in some of the serum enzymes. All of these studies are an attempt to discover a "biologic dosimeter" of radiation illness.

Symptomatic response to radiation has also undergone a change of interpretation. While previously we believed that nausea, vomiting and diarrhea would occur in patients receiving an acute total body dose of over 500 r.,[5] this idea is gradually being replaced. Again the change in thinking is due to experience with total body irradiation in terminal cases of malignancy. While it may be said that the patients who receive intentional total body radiation are cared for more meticulously and are sedated during the radiation treatment, compared with casualties in the field or at an accident site, it has been noted that patients can receive a lethal dose of radiation in a short period of time without exhibiting signs of nausea, vomiting or diarrhea. The epilation that appears apparently requires an air dose equivalent to about 300 to 350 r. of 100 to 200 kv. x-ray. While it is difficult to extrapolate this dose to an exposed dose of higher energy radiation, it has been noted that an instantaneous dose of cobalt-60, in the order of 600 to 700 r. in air, is enough to completely epilate an individual. Patients who were exposed uniformly to a 900 r. in air dose began epilation on the 12th to 15th post-therapy day and the epilation was complete approximately 48 to 72 hours later. Melena, when it did appear, appeared at a terminal stage approximately 4 weeks following the radiation therapy and was due to the bleeding tendency and not denudation of the gastrointestinal tract. Evidence of bleeding was seen in these cases and this was noted as petechiae and occasional ecchymoses which appeared about 3 to 4 weeks post-irradiation, although the platelet count in these patients had been below 20,000 for 2 to 3 weeks prior to these manifestations.

Problems Involved in Receiving and Admitting Radiation Exposure Patients

The type of radiation exposure and the dose received must be considered in procedures involved in receiving and admitting to the hospital patients exposed to a peacetime nuclear accident. In the case of a nuclear accident it would be best to admit all patients to the hospital immediately and carry out evaluation as will be described later in this paper. If the exposure is definitely known to be a gamma or a gamma-plus neutron exposure, such as might occur during a reactor excursion without rupture of the fuel capsule, the following recommendations involving decontamination of patients might be ignored. However, if the patients have been exposed to an accident which might or possibly may involve external contamination or internal contamination by radioactive materials, the following procedures relative to decontamination and segregation should be observed.[6]

In general, patients in the latter categories should be segregated into the groups according to their physical condition. An area should be set aside for the reception and examination which would include radiation monitoring of patients known to be exposed, or possibly exposed, to a radiation accident. This area should be in the hospital and might well be an isolation ward or a similar area which is not being used at the present time. If there is no such ward or area available, a portion of the interns' quarters or nurses' quarters which have numerous shower areas might be so designated as an emergency examination and decontamination area. Since we are speaking of peacetime accidents, such an area should have available a duplicate set of examination and shower spaces to accommodate both sexes. It goes without saying that personnel should be trained to monitor, examine and decontaminate individuals who have been or might have been exposed in case of a peacetime nuclear accident. The segregated groups of possibly contaminated patients should be cared for as shown in table 3.

TABLE 3

I. *Ambulatory Patients (uninjured).*
1. Monitor patients with clothes on. If not obviously contaminated, allow patient to temporarily leave area for later consideration.
2. If contaminated, remove clothing and dispose of clothing.
3. Refer patients to decontamination area for thorough washing under shower with a detergent and scrub brush.
4. Dry in shower room.
5. Monitor outside shower room. If still contaminated, repeat shower (clip hair, if necessary).
6. Dress in pajamas.
7. Go to area designated by doctor on duty.
8. Be available for further studies indicated by type of exposure (low background total body counting, hematological studies, radioassays of excreta, etc.).

II. *Ambulatory Patients (injured).*
1. If patient has first aid or temporary dressings, remove same and monitor as though he were uninjured.
2. If further first aid is needed, perform same.
3. If the bandages or first aid dressings that have been applied are soiled, etc., it might be necessary to remove the top layers and monitor as previously stated.
4. If the patient is contaminated, remove clothes, remonitor and dress in pajamas. Carry out any emergency treatment required.
5. If the patient is grossly contaminated and could withstand a cleansing shower, perform this procedure, then dress in pajamas and admit to the hospital. Perform additional studies as indicated by the type of exposure. (See I, 8.)

III. *Stretcher Patients (noncritical).*
1. Monitor patient. If not contaminated, remove clothing, apply pajamas and admit to hospital as a probable noncontaminated person.
2. If contaminated, remove clothing, take the patient to tub sink or tub bath, decontaminate as much as possible, dress in pajamas, and admit to hospital. Perform additional studies as indicated by type of exposure. (See I, 8.)

IV. *Stretcher Patients (critical).*
1. Administer necessary first aid.
2. Monitor as thoroughly as possible.
3. If they do not appear contaminated, treat as any other noncontaminated, critically injured stretcher patient, then admit to hospital.
4. If contaminated and in critical condition, wash surface area as much as possible and admit to hospital. Perform additional studies as indicated by type of exposure. (See I, 8.)

Over-All Procedure in Caring for Known Contaminated or Possibly Contaminated Individuals

All patients described in the foregoing paragraphs that are to be admitted to the hospital should be admitted to a segregated position in the hospital. An unused isolation ward would be ideal for this. If they were known to be contaminated they should be segregated as much as possible in one such group. If both sexes were involved, they should be handled in the customary manner. If they were not proven to be contaminated by cursory examination in the emergency room, they should be segregated in another portion of the hospital, and if both sexes are involved this should be taken into consideration.

The Problem of Publicity. One of the greatest problems concerning the hospital admission of patients exposed to peacetime radiation accidents will involve the relationship with the press. Perhaps the most lucid and intelligent description of this problem is given by Marshall Brucer in the report of the Y^{12} accident at Oak Ridge in 1958.[4] This is a problem for the hospital administration, but most certainly the doctors, nurses and technicians caring for these patients will be approached by the press for their comments and opinions. It is suggested that one read the report of the Y^{12} accident with particular reference to the comments in preparing for such possibilities.

Early Evaluation of the Radiation Exposure Patient

Clinical Examinations. Patients involved in a peacetime nuclear accident or incident should be considered in the same category as burn patients. Every department in the hospital might well be involved in the care of these patients. It is most important from the medicolegal standpoint, as well as the evaluation of the case, that a meticulous physical examination and history be undertaken as soon as possible. The physical examination should be of the same type as is given most patients with particular reference to the condition of the hair, skin, genitalia and reticuloendothelial organs. The history should include a background of past history related to incidents of cancer, and leukemia in the family as well as the immediate past history of the patient. It is extremely important that the exact position of the patient be obtained at the time of the accident and, in addition, any symptoms of the patient immediately following the accident should be described in detail. It is quite likely that if the accident were of a dramatic type, the symptoms of the patient would be magnified. These symptoms, however, should be recorded.

In cases described in this paper, probably as in no other type of patient, the laboratory studies are of extreme importance. The first study that should be performed is a complete hematologic study, including an accurate platelet account. If the patient was exposed to a large dose of radiation, a base-line bone

marrow study should be performed at once. It should be ascertained that a well-trained hematology technician performs this work, and moreover, that the same technician performs follow-up studies on the same group of patients in the ensuing days. While in previous reports the blood chemical studies have proven of not too much value, it is advisable that a complete battery of blood chemistry, liver and kidney function studies be performed upon arrival of the patient to the hospital. Urine studies should include a routine urinalysis as well as special studies.[4] It is unlikely that most laboratories will be able to carry out the more specialized studies, and since this is the case 24 hour urine should be saved, the volume measured, and aliquots frozen. Thus, later studies involving special amino-acids, etc., may be performed. Likewise, samples of serum of the blood should be frozen so special studies may be made by groups at other hospitals which are specialized in such studies.

There are several determinations that should be done if at all possible. If the patient has been exposed to neutron irradiation, such as might occur during a reactor excursion, or to internal contamination, the patient should be studied in a low background whole body counter. One medical center in the vicinity of a large power reactor or a group of reactors should be equipped with this type of apparatus. In these types of exposure it is important that the physician, who is to care for these patients, has available the following facts:

1. How much radioactivity is present in the body.

2. What kind (gamma ray energy) of radioactivity is present in the body.

3. Where this radioactive contamination is located in the body.

4. What and how much radioactive material was induced by neutron activation of the patient's tissues.

The above listing should be apparent as to their importance. This type of analysis can be obtained only by whole body counting.

Other special studies should include breath analysis in the case of known or possible inhalation of radioactive materials. Such types of analyses are carried out by the National Bureau of Standards in Washington, D. C. If the contamination might have resulted from the ingestion or inhalation of the fuel of the reactor, or a nuclear weapon, analysis of the urine for plutonium may be indicated.

Continued Evaluation of the Patient Exposed to Radiation

Maintenance of Clinical Status. Daily examinations of patients exposed, or probably exposed, to nuclear accidents should be carried out as long as indicated. If the patient has definitely been exposed to a nuclear accident, the examination should be carried out for an extended length of time as indicated by the type of exposure and dosage of radiation. Special attention should be given to the hair, as to the time and extent of epilation. If the patient is known to have been exposed to a large dose of radiation, examination should include the signs of the onset and duration of hemorrhagic diathesis. If the patient has been exposed to neutron irradiation, examination of the lens of the eye should be done at the earliest practicable time and continued examination at 3 to 6 month intervals for a period of several years. This examination, of course, should be performed by slit lamp microscopy. If the patient has been exposed to a large dose of any type of ionizing radiation of a penetrating nature (1. and 2., Table 2), continued examination of the sperm for motility and viability should be made at periods as indicated. If the exposure was localized, as to a particle accelerator of some type, it might be advisable to biopsy the skin, or perhaps other structures for histologic and pathologic examination of the tissues.

Laboratory studies should be carried out as described previously. Continued hematologic examination of the peripheral blood and also of the bone marrow should be performed, preferably by the same technician, at periods indicated by the pathologist or the hematologist. Twenty-four hour urine collections should be continued as long as the patient manifests signs and symptoms of his radiation illness. If the patient was exposed to neutron activation or inhaled or ingested radioactive materials, repeated studies in the low background counting chamber would indicate the effective half-life of the radioactive materials deposited into or induced in the body. Likewise, continued examinations of the urine in the case of the entrance of plutonium into

the body, may again indicate the effective half-life of these materials as well as the effect of special therapeutic measures.

Management and Treatment of Patients Exposed to Radiation

The most important procedure involving the care of severely irradiated patients is that of meticulous nursing care. Thus, the training of a corps of registered nurses and ward attendants in the field of Nuclear Nursing is of primary importance.

Patients who have been exposed to what has been considered to be a dose of ionizing radiation above the LD-50 range, should be provided with meticulous nursing care in a near sterile environment.

At the present time we have no specific or definitive therapy for the treatment of patients exposed to radiation. Several new methods have been attempted during the past 2 or 3 years, but as yet none have proven themselves specific. I will list several methods of management but do not mean to indicate that they are listed in the order of their importance.

The first is the problem of blood replacement and platelet transfusion. As indicated previously, experience with total body radiation therapy does not show that the platelets reached their lowest ebb at the end of 28 days as has been stated from extrapolation of animal studies. Rather, the white blood cells and platelets appear to disappear more rapidly as the radiation dose increases. The need for platelet transfusions is not apparent, usually, for 3 or 4 weeks during which time the platelet count has been at a consistently low level. Some groups, who are performing total body irradiation in terminal cancer and leukemia, believe in administering fresh platelet transfusions at regular intervals, prior to symptoms of a hemorrhagic diathesis, and this may well be the most opportune method of combating these hemorrhagic tendencies in severely irradiated cases. The need for blood transfusions rests upon the total red blood cell mass as best determined by measurements of the peripheral blood.

The question of when and what type of antibiotics to administer is still open to conjecture. It is best to perform meticulous bacteriologic cultures of the throat, sputum, urine and feces and then combat these organisms after they have been tested with specific antibiotics. The vast fields of virology and mycotic diseases are at this time almost untouched in studying the treatment of infections occurring in the total body radiation victim.

One of the most important measures that can be accomplished early in the treatment and management of patients exposed to large doses of ionizing radiation is the maintenance of fluid and electrolyte balance. This is a relatively simple procedure to which most hospitals are accustomed. It cannot be emphasized too greatly that fluid and electrolyte balance in the patient exposed to radiation is very important.

The use of bone marrow transfusion in patients who have received a near lethal or lethal dose of radiation has been extensively studied, and at the time of the writing of this paper the results are still somewhat vague. While there have been indications that homologous marrow transplants resulted in an increase in the peripheral blood count of the recipients,[7] this has not yet been fully accepted. Some patients, who have had intentional total body radiation and who have received isologous and autologous transplants, have no doubt had their condition improved following such treatment. In any case, the types of bone marrow transplants that have proven most effective in the human were performed with fresh bone marrow. Fresh bone marrow is defined as bone marrow that has been given immediately following its reception from the donor, or which has been stored for a few days in a nutrient media. There has been some evidence in the human that preserved autologous bone marrow has been effective in the management or treatment of patients exposed to radiation.[8] This is considered one of the most important possibilities in planning for the care of individuals working in the vicinity of a high power nuclear reactor.

In addition it has been indicated that cell free extracts may be effective in combating the effects of lethal or super-lethal exposure in ionizing radiation.[9] Again, most of this data has accumulated from animal experiments and to my knowledge there has been no human experience in this regard.

If the patient has received, either intentionally or accidentally, bone seeking radioiso-

topes, such as radium, thorium, plutonium, or strontium, there is one method of eliminating at least a portion of the radioactive material from the bone. This has been by the intravenous administering of a chelating agent. This agent, forming a complex with the radioactive material, removes it from the bone and permits excretion in the urine. Such agents have been used in combating the effects of lead poisoning, as well as in a few accidents involving plutonium and strontium toxicity of the human.[10,11]

If chelating agents are used to remove the radioactive contaminants from bone, it might be wise to employ an artificial kidney to assist the natural kidneys in liberating these materials from the circulating blood.

Requirements for a Facility to Manage Patients Exposed to Radiation

Personnel. Under this general paragraph there will be several recommendations which need not mean that permanent and specific requirements be set up in desired medical centers. Rather, existing facilities and personnel could be utilized, and in a few instances new apparatus would be required to care for this type of patient. A medical center which is in the vicinity of a power reactor, or other potential sources of a radiation accident, should have trained personnel who would work as a team. This team should, of course, have as its head a trained physician, preferably a radiologist, who is well versed in the dosimetry, effects, and the science of radiation. In addition to the leader, one or more additional physicians should be trained and standing by on this team. The number of physicians required depends upon the potentiality of the immediate area for radiation accidents.

Nurses trained in nuclear medicine are very important members of the main group. These nurses should have experience and background in the handling of patients who receive radiation therapy and routine radioisotope studies or treatment. The nursing profession is at the present time awakening to the responsibility in this field, and is making great strides in attempting to train members of their profession in the care of radiation patients.

Another important member of the team is the radiation physicist. The radiation physicist is really the key member of the team who will attempt to estimate the dosage that the patients might have received.

Also important in this team of personnel are the radioisotope technicians. These technicians will be asked to perform radioassays upon the excreta and blood of the patient, as well as carry on the routine monitoring involved in decontaminating the patients and in measuring the induced radioactivity by whole body counting. Specialized hematology technicians and chemistry technicians also are required. These will be called upon to do the more technical determinations of urine and blood which will involve, in many cases, chromotography and ion exchange procedures.

Space Requirements. As indicated previously, a receiving area should be set aside so these patients may be brought into the hospital in an orderly manner, be examined, decontaminated if necessary, and be admitted to the hospital. Such a receiving area need not be a locality reserved for this special type of examination, but might well be a ward in use at the time, or quarters reserved for members of the hospital staff. Plans should be made for a ward space to receive such patients, and if foresight were used, ward space for both males and females would be included in the hospital plans. Again, these wards would probably be used routinely for other types of patients, but should be adjacent to the proposed receiving area so they may be cleared very rapidly in the case of an accident, and thus be used entirely for reception and care of radiation patients. Likewise, laboratory facilities for the special studies involved should be available.

Special Equipment. In the situation mentioned in the above paragraph, it would be desirable to have a low background counting room available. These are of two general types, one which will count quite rapidly the total radioactivity in the patient's body, and another which will count at a much slower rate, probably one hour, the type of radiation present. The latter process is achieved by a multichannel gamma ray spectrometer. The cost of both types would total in the vicinity of $50,000.00 to $75,000.00.

The hospital or medical center, which is to be designated as a possible receiving center

following radiation exposure, should have in its confines an active blood bank. This blood bank should be capable of offering services around the clock as well as being able to offer fresh platelet transfusions. It may be advisable to have an adjacent tissue bank for the storage of autologous and isologous marrow, if they are proven definitely effective. This tissue bank should be equipped to store this type of marrow for a period of months, by whatever method will be found necessary for preservation.

The important duty for any institution which is planning to establish a team, and secure the space and equipment to care for such patients, is to instigate interest in the local medical profession. If the doctors in the area are not interested in the problem of radiation contamination, and in the problem of caring for patients who have been exposed to ionizing radiation through peacetime accidents, then any accident that may occur in the future will not be met in the best possible manner. It should not be necessary to point out to the medical profession that the planning for such situations is a large step toward training of members of our profession and its allied groups for possible use in the event of a future war employing nuclear weapons.

Studies Ancillary To This Facility

One of the many questions that individuals will ask when confronted with this detailed and rather elaborate plan is, "What will these people and this equipment be used for while you are waiting for a nuclear accident?"

It would seem that one with foresight, and with experience in clinical investigation, could think of a multitude of problems to which such a facility might be applied during the waiting period. Some of these are the routine clinical studies with radioisotopes. If a laboratory had a shielded ion room for low background whole body counting, it could be utilized for routine isotope studies such as thyroid uptake, radioiron studies, and the like. By the use of shielded room it is possible to reduce the dose of radioactivity for routine clinical studies by as much as a factor of 10, and to eliminate many of the present steps in clinical radioisotope work. In addition, the patients treated by routine radiation therapy could be studied regarding the effects of radiation on the enzyme systems, excretion of special amino-acids, and the like. Thus, the meager amount of information now available on the effects of radiation on the hematologic and enzyme systems of the human patient could be increased immeasurably. Another type of study that could be performed in a routine measure is that of dosimetry of both animals and humans. Last but not least, in centers which are now pursuing the use of total body radiation therapy, there would be a wealth of information available from patients treated in this manner to better evaluate the effects of radiation on the human.

Summary

A method of caring for patients who have been exposed to a peacetime nuclear accident has been described. It should be apparent that the preparation for such an accident, and experience of the medical team, if such an accident should occur, would better prepare the medical profession to cope with problems resulting from a nuclear attack.

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Hemorrhagic Diathesis Associated with Long-Term Anticoagulant Therapy*

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The bleeding tendency which may manifest itself during anticoagulation treatment is not related to a specific coagulation defect, but may involve multiple factors. Vitamin K is valuable in the control of such bleeding.

THE HEMORRHAGIC DIATHESIS associated with long-term anticoagulant therapy in patients with "therapeutic" prothrombin times, occurs with unrecognized frequency.[1] In this investigation, the coagulation defects were determined in patients with this type of bleeding. In addition, long-term observations are recorded of the coagulation defects in two patients on anticoagulant therapy. Correction of these defects has been rapidly effected *in vivo* by vitamin K_1.

Materials and Methods

Selection of Patients. The patients under investigation had been on continuous anticoagulant therapy for periods greater than 6 weeks and were bleeding at the time of study. This group consisted of 25 patients examined weekly in the Out-Patient Clinic of Jackson Memorial Hospital and 10 private patients seen at varying intervals. Most of the patients had arteriosclerotic heart disease with a past history of myocardial infarction and many patients had more than one previous myocardial infarction. The severity of the cardiac disease and its management were not taken into consideration in evaluating the data obtained in this study, but was comparably similar.

Control specimens were obtained from normal individuals. Sera from patients with known PTC., Stuart-Prower factor,* Factor VII,** and Hageman*** factor deficiency were used, as indicated under **"Results."**

Coagulation Studies. Venous blood was collected from nonfasting patients. Blood allowed to clot in glass test tubes at 25°C. was used to determine the clotting time. Aliquots of the serum obtained from the specimens were incubated at 37°C. for 4 hours after clotting for the thromboplastin generation tests. Plasma was obtained from whole blood to which 0.1 M. potassium oxalate solution had been added. Plasma and serum were separated by centrifugation at 3,000 r.p.m. at 25°C. for 15 minutes. A detailed description of the methods has been described previously.[2]

Results

The 35 patients studied had been on long-term anticoagulant therapy (Dicumarol, warfarin sodium, phenprocoumon, or 2-phenyl-1, 3-indandione). Blood specimens from these patients were obtained within 48 hours of the onset of clinical recognition of the bleeding and prior to specific treatment for the bleeding. The most frequent types of bleeding were purpura, bruising, and hematuria. Bleeding from the genital tract, subconjunctival hemorrhage and bleeding into the joints was also noted. No instances of fatal hemorrhage occurred in this group of patients.

Coagulation Studies in Patients Bleeding

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*Courtesy of Dr. John Graham, Department of Pathology, University of North Carolina School of Medicine, Chapel Hill, N. C.

**Courtesy of Dr. Harold A. Wurzel, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

***Courtesy of Dr. Oscar Ratnoff, Department of Medicine, Western Reserve School of Medicine, Cleveland, Ohio.

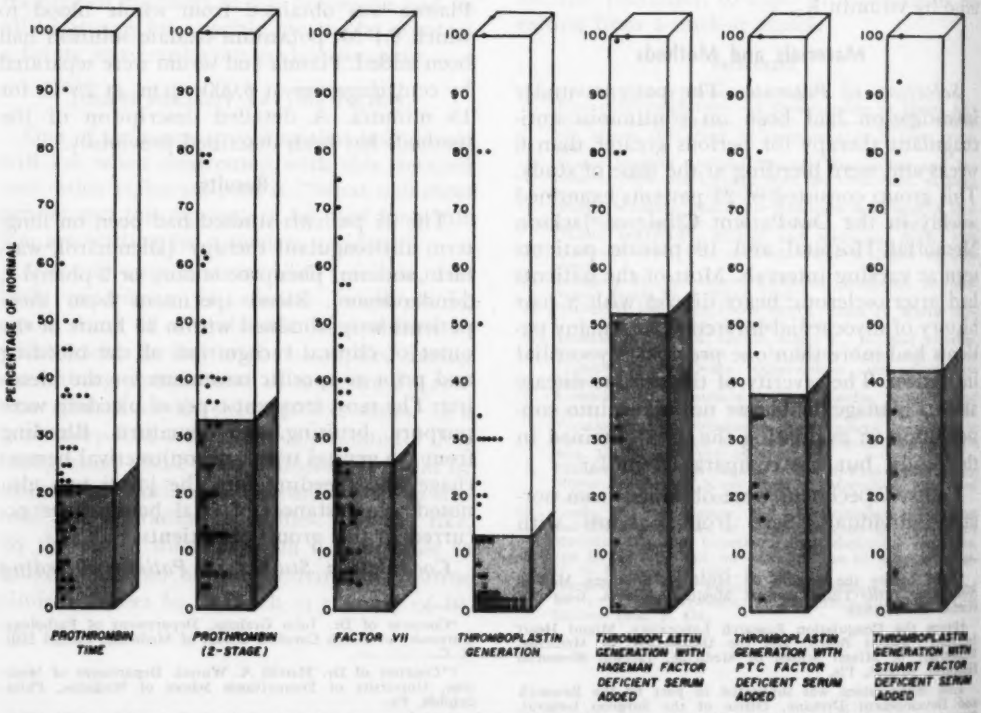
from Anticoagulants. Complete coagulation studies were done in 35 patients on long-term anticoagulant therapy with a total of 41 bleeding episodes. Figure 1 illustrates the data obtained. The individual results are plotted as percentage of normal while the average values in each test are represented by the shaded area of the bar graphs. The average prothrombin time, prothrombin, Factor VII, and thromboplastin generation test is: 21%, 34%, 25% and 12%, respectively. Partial correction of the patient's abnormal thromboplastin generation test is effected by adding either PTC. deficient serum, Stuart factor deficient serum, or Hageman factor deficient serum. Complete correction of the abnormal thromboplastin generation test was obtained with PTA.* deficient serum, Factor VII deficient serum and normal serum,** when added individually in a 50% mixture to serum from the anticoagulant patients.

*Plasma Thromboplastin Component.
**Unpublished data.

Serial Observations of Coagulation Defects in Patients on Long-term Anticoagulant Therapy. The different coagulation factors of a patient maintained on Dicumarol therapy for the past 18 months is shown in figure 2. Three episodes of hemorrhage are included. During three bleeding episodes the thromboplastin generation is below 10 per cent. Prothrombin and Factor VII were less than 20% in two hemorrhagic phenomena but were 25% and 40%, respectively, while the patient had "spontaneous" bruising.

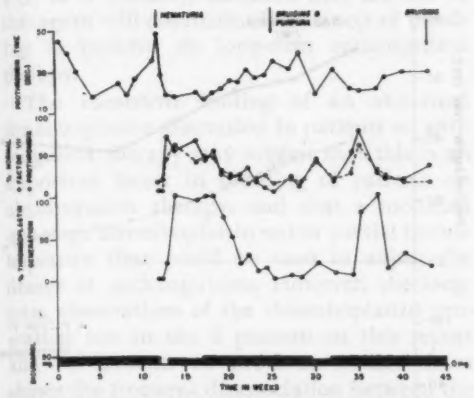
Another patient on long-term warfarin sodium therapy for the past two years is shown in figure 3. During two bleeding episodes his prothrombin time was 20 seconds, prothrombin was greater than 25%, Factor VII was 10% and thromboplastin generation was less than 25 per cent. During the period of 35 weeks illustrated, the prothrombin time was often below the therapeutic range and was never greater than 29 seconds. In both these patients, it will be noted that there was

FIG. 1



The effects of long-term anticoagulant therapy on the coagulation factors in patient's bleeding. The shaded areas represent the average percentage values for the various tests. The dots represent the actual value obtained in the specific tests.

FIG. 2

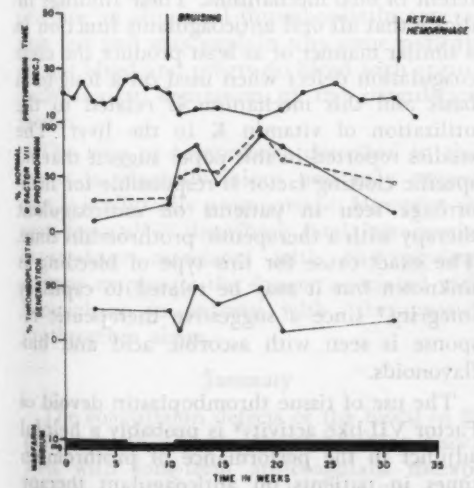


The relative levels of the various coagulation factors in a patient on long-term Dicumarol therapy. The rapid (rebound) of SPCA and prothrombin (two stage method) are in marked contrast to the sluggish return of the thromboplastin generation test to normal.

a rapid increase in Factor VII towards normal after stopping or reducing the dosage of the anticoagulant. Prothrombin increased at a slower rate than did Factor VII, while the serum thromboplastic factors returned to normal several days after the change in therapy.

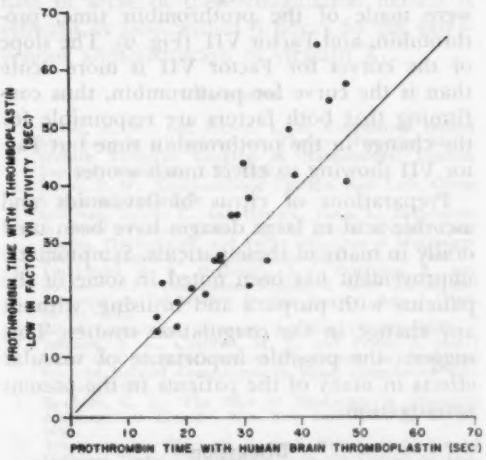
Importance of Factor VII Activity in Tissue Thromboplastin and Prothrombin Time in Patients Bleeding from Anticoagulant Therapy. Prothrombin times were determined simultaneously with two preparations of tissue thromboplastin. One preparation* was shown to be low in Factor VII activity by assay with a fresh plasma obtained from a patient congenitally deficient in Factor VII. The prothrombin time with the human brain thromboplastin was 38 seconds while the prothrombin time with the commercial thromboplastin was 100 seconds. The control prothrombin times were 12 seconds and 14 seconds, respectively. The data obtained with these two thromboplastin preparations is shown in figure 4. It is apparent that the Factor VII content in the thromboplastins does not affect the prothrombin times remarkably in this group of patients, with the possible exception of prothrombin times greater than 30 seconds.

FIG. 3



The relative independence of the various coagulation tests on a patient on long-term warfarin therapy. Note the dissociation between the prothrombin factors and thromboplastin generation curves.

FIG. 4


PROTHROMBIN TIME WITH THROMBOPLASTIN LOW IN FACTOR VII ACTIVITY (SEC.)
PROTHROMBIN TIME WITH HUMAN BRAIN THROMBOPLASTIN (SEC.)

Comparison of the prothrombin times with two preparations of thromboplastin obtained in patients bleeding from anticoagulant therapy.

Effect of Vitamin K_1 on the Hypoprothrombinemia Associated with Anticoagulant Therapy. The effect of an intravenous injection of 5 mg. of vitamin K_1** on the prothrombin times of 20 patients who were on long-term anticoagulant therapy is shown in figure 5. Within one hour the average prothrombin time is reduced from 40 seconds to 30 seconds and after 6 hours the average prothrombin time is 20 seconds. To evaluate the relative importance of prothrombin and Factor VII on this reduction in prothrombin times a similar study was done in two patients by the intramuscular administration of 5 mg. of vit-

*Acuplastin, Ortho Pharmaceutical Company, Raritan, N. J.
**Mephyton, Merck Sharp & Dohme.

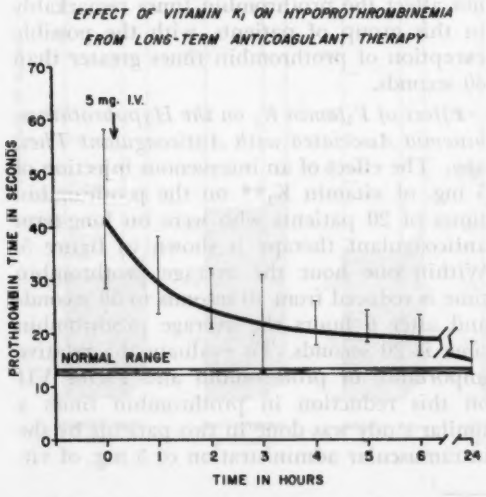
amin K_1. In this study, serial observations were made of the prothrombin time, prothrombin, and Factor VII (Fig. 6). The slope of the curves for Factor VII is more acute than is the curve for prothrombin, thus confirming that both factors are responsible for the change in the prothrombin time but Factor VII showing its effect much sooner.

Preparations of citrus bioflavonoids and ascorbic acid in large dosages have been used orally in many of these patients. Symptomatic improvement has been noted in some of the patients with purpura and bruising, without any change in the coagulation studies. This suggests the possible importance of vascular effects in many of the patients in the present investigation.

Discussion

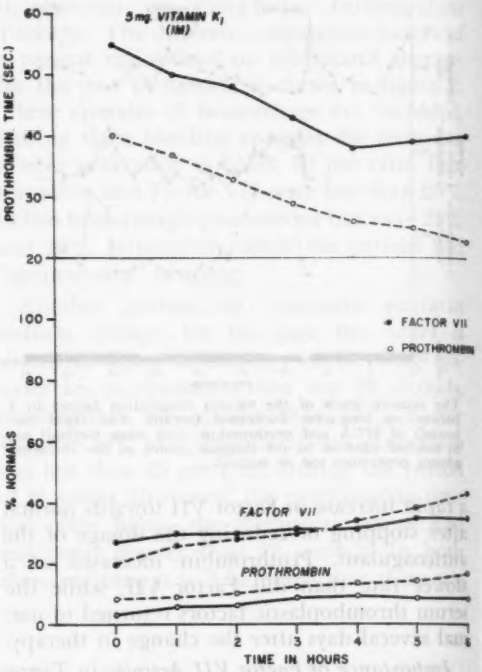
The results of this study are similar to the findings previously reported from this Laboratory in 300 patients on various long-term anticoagulant regimen. Thus the average reduction in prothrombin, Factor VII, PTC. factor, Stuart factor, and Hageman factor is approximately the same in patients on long-term anticoagulant therapy in blood specimens done at random or while there is clinical bleeding. These findings taken together with recent reports on the coagulation defects in patients with vitamin K deficiency[8] and with severe liver disease[4] allows one to correct a

FIG. 5



The average effect of vitamin K_1 on the prothrombin time in 20 patients on anticoagulant therapy.

FIG. 6



The effect of intramuscular vitamin K_1 on the prothrombin time, prothrombin, and Factor VII in two patients with hypoprothrombinemia due to long-term anticoagulant therapy. Note that Factor VII increased more rapidly than prothrombin.

view expressed in the literature 2 years ago[5,6] suggesting that anticoagulants may act by different *in vivo* mechanisms. These findings indicate that all oral anticoagulants function in a similar manner or at least produce the same coagulation defect when used on a long-term basis and this mechanism is related to the utilization of vitamin K in the liver. The studies reported in this paper suggest that no specific clotting factor is responsible for hemorrhage seen in patients on anticoagulant therapy with a therapeutic prothrombin time. The exact cause for this type of bleeding is unknown but it may be related to capillary integrity,[7] since a suggestive therapeutic response is seen with ascorbic acid and bioflavonoids.

The use of tissue thromboplastin devoid of Factor VII-like activity[8] is probably a helpful adjunct in the performance of prothrombin times in patients on anticoagulant therapy since this will more correctly reflect the combined depression of prothrombin and Factor

VII. It is unlikely, however, that the use of this agent will eliminate all instances of bleeding in patients on long-term anticoagulant therapy.

The consistent finding of an abnormal thromboplastin generation in patients on anticoagulant therapy may suggest that this is an important factor in bleeding of patients on anticoagulant therapy, and that a modified one-stage thromboplastin test or partial thromboplastin time could be used to adjust the dosage of anticoagulants. However, the long-term observations of the thromboplastin generation test in the 2 patients in this report and on patients in previous studies[9] have shown the frequent disassociation between the level of the prothrombin forming factors and the thromboplastic factors. However, use of data from both the prothrombin time and thromboplastin generation may identify the potential bleeding patients from the non-bleeders.

The importance of Hageman factor as a cause of hemorrhage is not known. Recent reports[10,11] have established that Hageman factor is different from PTA. factor and the cross matching studies of the thromboplastin generation test in this report support these findings. Patients congenitally deficient in this factor do not bleed abnormally. Therefore, the importance of Hageman factor as a cause of hemorrhage in the present study is not clear. However, Hageman factor[12] does produce an abnormal thromboplastin generation test and may explain why some patients do not bleed and others do bleed with apparently similar depression of the coagulation factors.

The type of hemorrhage described in this report is generally minor and may suggest that it is clinically unimportant. However, recent reports[13-15] describing fatal intracranial hemorrhage associated with anticoagulant therapy emphasize the danger associated with hemorrhage in patients with "therapeutic" prothrombin times.

Summary

The coagulation defects of the blood of 35 patients with 41 episodes of bleeding associated with long-term anticoagulant therapy have been studied. A multiple deficiency of factors is associated with the hemorrhagic diathesis observed in these patients. Correction of some of these coagulation defects is effected *in vivo* within 6 hours by the intravenous administration of vitamin K_1.

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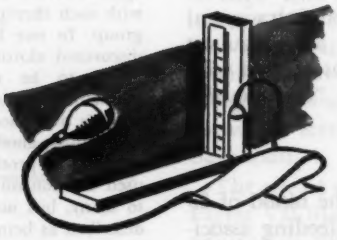
Discussion (Abstract)

Dr. Kenneth M. Brinkhous, Chapel Hill, N. C. Dr. Boyles' presentation provides us with a detailed analysis of many of the changes which occur in the plasmatic clotting factors following Dicumarol-indanedione therapy. The general belief today is that these drugs act as an antivitamin K, their effect being mediated through the mitochondria, particularly in liver cells, by depressing the synthesis of a number of coagulation proteins. Initially, only hypoprothrombinemia was recognized. But over the years, additional procoagulant factors have been described as being depressed with such therapy. Later Factor VII was added to the group. In our laboratory not long ago, the recently discovered clotting factor, Stuart factor, likewise was found to be depressed in anticoagulant therapy (Graham, Hougie, and Barrow). Christmas factor, likewise, is depressed and today we hear that Dr. Boyles has added another factor, Hageman factor, to this group. The prothrombin time test which is ordinarily used for control of anticoagulant therapy is sensitive to many, but not all, of the factors which have been described as being depressed with these drugs. Depression of Christmas factor, for example, does not influence the prothrombin time test. This may well be the variable that Dr. Boyles is observing in his comparative studies with the prothrombin time test and the thromboplastin generation test, the latter being sus-

ceptible to changes in Christmas factor. This is of considerable interest today because of suggestions that Christmas factor may be highly important in the pathogenesis of the thrombotic process.

In our own studies we have devised a simple one-stage test which we have called the *partial thromboplastin* time, or PTT. for short. We have used this test in a manner similar to Dr. Boyles' use of the thromboplastin generation test. The PTT. test avoids one of the difficulties of the thromboplastin generation test, namely, the need for a serum reagent, which is particularly difficult, if not impossible, to standardize. The partial thromboplastin time is also sensitive to changes in all of the recognized procoagulants, including antihemophilic factor and Christmas factor. The PPT. appears to provide a better method for indicating the over-all clotting ability of plasma where there is simultaneous depression of several coagulation factors as occurs in a number of circumstances, including Dicumarol therapy. The time for coagulation with this test is approximately 60 seconds for normal plasma, in contrast to the 12 to 14 seconds for the prothrombin time. The test is as easy to perform as the prothrombin time. And in our hands it has been actually more sensitive to depression of plasma procoagulants than the thromboplastin generation test. We would be interested to see how results with the partial thromboplastin time would compare with the other tests that Dr. Boyles has performed in these patients on long-term anticoagulant therapy.

In regard to hemorrhage in patients on anticoagulant therapy, we have not been impressed that this is as an important complication when the dosage of the drug is regulated to give a prothrombin time between two to two and one-half times the control prothrombin time value. The serious hemorrhages which we have encountered have been mainly in 3 types of patients: (1) those patients who for one reason or another are unable to co-operate fully and take an overdose of the drug; (2) the patients who are usually sensitive to the drug, and who rapidly develop a hemorrhagic tendency; and (3) occasionally in patients who have continued taking the drug without any laboratory checks at all. Dr. Boyles is referring, of course, to another group of patients, those who have hemorrhage while the prothrombin time value is within the so-called therapeutic range. His studies in a way emphasize the enigma of the hemostatic mechanism. We have been impressed in the laboratory that surgical procedures can be carried out on dogs under the influence of Dicumarol therapy, without presenting any special bleeding problems. This same observation has been made by others with patients who have had operations while under Dicumarol therapy; abnormal bleeding did not occur in spite of the presence of a continued hypocoagulable state. It appears that nature has provided man with a hemostatic mechanism in which there is a wide margin of safety. Three major components of this system have been emphasized: fibrin coagulation, platelets, both quantitative and qualitative aspects, and integrity of the smaller vessels, particularly the micro-circulatory system. It appears from both experimental and clinical experience that at least two of the three factors must be altered before significant hemorrhage occurs (Jaques). Since Dicumarol type therapy affects predominantly the fibrin coagulation mechanism, it may be that transient changes in the other two systems, possibly unrelated to the therapy itself, become the determining factor as to whether or not hemorrhage occurs in patients during controlled anticoagulant therapy.



Studies Relating to Creeping Eruption*

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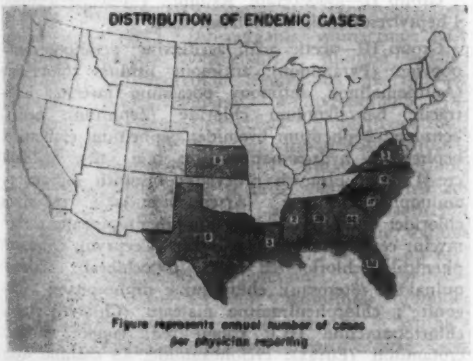
The treatment of creeping eruption is still unsatisfactory. The authors have tried out many substances in the hope of finding a satisfactory therapeutic agent, but without definitive results.

Introduction

CREEPING ERUPTION due to the intracutaneous migration of the larvae of the cat and dog hookworms *Ancylostoma braziliense* and *Ancylostoma caninum* continues to be a problem of considerable magnitude in the southeastern and gulf states.

This is pointed up by the fact that there were over 7,000 *reported* cases in Florida alone in 1950.[1] Another indication of the importance of the disease is offered by the replies to a questionnaire which we distributed to approximately 300 dermatologists in 48 states in 1956 (Fig. 1). By this we found that a dermatologist in Florida usually encounters 52 endemic cases annually, in Georgia 52, diminishing northward to 3 in Virginia, and westward to 5 in Texas. An interesting result of our survey which we have not seen mentioned before is that the Negro is relatively immune to creeping eruption. The replies to our questionnaire revealed that an estimated 95% of the patients were white, 5% being Negro. When one considers that the bulk of the patients are from regions with a high negro population, this is a striking difference. Perhaps it is a true racial partial immunity. It has been repeatedly shown that the Negro is somewhat resistant to *human* hookworm.

FIG. 1



The states designated "?" reflect an unresolved conflict in reports.

Those of us who, because of geographical position, have to live with this affliction, might be pardoned for waxing and waning periods of enthusiasm for various systemic treatments. However, most of us have ultimately been disappointed with the very methods which we have espoused. The lack of effectiveness of several systemic treatments was very nicely demonstrated statistically by Loewenthal,[2] in 1954. Nevertheless, it is still important that a search for an effective and practical method of treatment for this disease carries a high order of importance in the South.

It is to be emphasized that the studies presented here refer only to the common creeping eruption of the southern United States generally attributed to *A. braziliense* or *A. caninum*, and that in all of the experimental work reported here only the larva of *A. caninum* was used because it was readily available and thought probably to reflect also the characteristics of *A. braziliense*. We do not infer a parallel response of other larvae which may cause a "creeping eruption" in man, such as those of *A. duodenale, Necator americanus, Uncinaria stenocephala, Bunostomum phlebotomum,* and *Strongyloides stercoralis,* a group fully reviewed by Beaver[3] in 1956, and in the case of *S. stercoralis* reported by Arthur and Shelley[4] in 1958. Likewise this report has no bearing on the eruption caused in humans by the adult dog heartworm *(Dirofilaria immitis)* recently discussed by Sams and Beck.[5]

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These studies are largely *in vitro*, but some *in vivo* efforts to find a method which is toxic for the larvae of *A. caninum* on the one hand and tolerable to the human host on the other. It should be said at the outset that no such agent has been discovered, but we believe that this report at least may serve to point out many avenues which have been unrewarding and a few which perhaps show promise.

Materials and Methods

In Vitro Investigation of Chemicals.

The usual method of cultivating and preparing larvae employing the Baermann apparatus was the same as that used by Ritchie and King,[6] studying a mixture of *A. caninum* and *A. braziliense*, and in the quite recent report of Blank, Winter and Beck[7] employing *A. braziliense*. The studies reported here are essentially a duplication and continuation of theirs. One point concerning the preparation of the suspensions of larvae perhaps deserves emphasis. That is, that a small air space in the well of the slide should be provided when larvae are to be exposed to a test chemical. Von Brand[8] has shown that these organisms are essentially aerobic. We employed straight wall micro-concavity slides (hereinafter designated "well slides"), the well being 3 mm. deep and 16 mm. in diameter, with a volume of 0.6 ml. Into this well were placed 2 drops of water containing between 30 and 40 larvae. Four drops of the chemical solution to be tested were then added, which volume almost filled the well but allowed a small air space when closed with a sealed cover slip. If this air space was omitted, the larvae frequently became sluggish within a few hours, a factor which might produce misleading interpretations regarding the toxicity of the chemical being tested.

The dilutions of the various chemicals, when in contact with the larvae, were entirely arbitrary, depending on solubility or on estimation of "strength," and ranged between 0.05 and 0.005%. Each chemical was subjected to 2 or more examinations and usually several dilutions were employed. The diluent was most commonly distilled water, but in some instances solution was effected by altering the pH or employing other frequently used solvents. Complete absence of motility of all of the larvae was interpreted as death. Continuous controls consisted of suspensions of larvae in the same diluent used for the chemicals being tested.

TABLE 1

CHEMICALS LETHAL WITHIN 1 HOUR

Iodine
Pyridine
4-N-hexylresorcinol
4-isohexylresorcinol

Since this group of experiments was largely a "screening procedure" covering a wide range of chemicals, no satisfactory classification could be achieved. Those tested are therefore presented in a footnote,* grouped as to observed toxicity for *A. caninum* by this method of study, and are classified as, (1) chemicals which "killed" wtihin one hour, (2) those which "killed" within 12 hours (Tables 1 and 2), and (3) those which failed to render the larvae immobile within 12 hours.

TABLE 2

CHEMICALS LETHAL WITHIN 12 HOURS

Iodoacetate sodium
4-N-decylresorcinol
4-heptylresorcinol
4-octylresorcinol

*Group I—iodine (elemental); pyridine; 4-n-hexylresorcinol; 4-isohexylresorcinol.

Group II—iodoacetate sodium; 4-n-decylresorcinol; 4-heptylresorcinol; 4-octylresorcinol.

Group III—acetic acid; acriflavine; actidione; aminoprine (Pyramidon); antimony lithium thiomalate (Anthiomaline); antimony potassium tartrate; bacitracin; benzalkonium chloride (Zephiran); benzyl benzoate; bephenium bromide; bephenium embonate; bephenium hydroxynaphthoate; bile salts; brilliant cresyl blue; bismuth salicylate; bismuth sodium p-aminophenylarsonate (Arseno-Bismulak); cadmium chloride; cadmium oxide; cadmium propionate; carbomycin; cetyl pyridinium chloride (Ceepryn); chloramphenicol; chloriodized oil (Iodochloral); chloroquinaldol (Sterosan); chloroquine diphosphate; "Calgonite"; chlorpheniramine maleate (Chlortrimeton); chlortetracycline HCl; congo red; copper sulfate; crotamiton (Eurax); cyclohexamide; 15 cyanine dyes as follows: 2-(*p*-dimethylaminostyryl)-1-methylnaphtho [1,2]thiazolium chloride; 8-chloro-2-[2-(2,5-dimethyl-1-phenyl-3-pyrrl)vinyl]-1-methyl-quinolinium chloride; 2-[2-(1-amyl-2,5-dimethyl-3-pyrrl) vinyl]-1,6-dimethylquinolinium chloride; 2-[2-(2,5-dimethyl-1-phenyl-3-pyrrl)vinyl]-1,3,3-trimethylpseudoindolium bromide; 1,6-dimethyl-2-(*p*-dipropylaminostyryl)-quinolinium chloride; 2-[2-(2,5-dimethyl-1-*p*-phenetyl-3-pyrrl)vinyl]-1,6-dimethylquinolinium chloride; 2-[*p*-heptylmethylamino)styryl]-1,6-dimethylquinolinium chloride; 2-[2-

(2,5-dimethyl-1-phenyl-3-pyrryl)vinyl]-1-(2-ethoxyethyl)-6-methylquinolinium chloride; 2-[2-(2,5-dimethyl-1-phenyl-3-pyrrl)vinyl]-1-phenylquinolinium chloride; 1-(2-ethoxyethyl)-2-{3-[1-ethoxyethyl)-2(1)-quinolylidene]propenyl}-quinolinium chloride; 2-[2-(1-amyl-2,5-dimethyl-3-pyrrl)vinyl]-1-methylbenzothiazolium chloride; 2-[2-(1-amyl-2,5-dimethyl-3-pyrrl)vinyl]-6-methyl-1-propylquinolinium chloride; 2-[2-(1-amyl-2,5-dimethyl-3-pyrrl)vinyl]-1-methylnaphtho[1,2]thiazolium chloride; 3-[3-(2,5-dimethyl-1-phenyl-3-pyrrl)allylidene]-2,5-dimethyl-1-phenyl-3-pyroleninium chloride; 1-(2-ethoxyethyl)-2-{3-[1-(2-ethoxyethyl)-6-methyl-2(1)-quinolylidene]-propenyl}-6-methyl-quinolinium chloride; dichloro diphenyl trichloroethane (DDT); diethyl aminoacetal; diethylaminol sodium antimony gluconate (Stibanose); diethylcarbamazine (Hetrazan); diethylstilbestrol; di-iso-propyl fluorophosphate (Floropyrl); dithiazanine iodide; di-iodohydroxyquin (Floroquin); dimethyl aminoacetal; emetine HCl; endomycin; erythromycin; erythromycin lactobionate; ficin; fluorescein; hyaluronidase; hydroquinone; hydroxystilbamidine; iodized oil (Lipiodol); iodochlorhydroxyquin HCl (Vioform); isoniazid; leche de hugueron (latex of Ficus laurifolia); lucathone HCl (Nilodin); mechlorethamine HCl (Mustargen); methyprylon (Noludar); methylene blue; monoethanolamine para-amino-benzoate (Nigenol); naphuride; neoarsphenamine; neutral red; nicotinic acid; nile blue; onion juice; o,o-diethyl o-p-nitrophenyl thiophosphate (Parathion); oxophenarsine HCl (Mapharsen); oxytetracycline HCl; pamaquine naphthoate (Plasmochin); papain; para-aminosalicylate sodium; penicillin G potassium; penicillin G sodium; pentaquin phosphate; petroleum benzin; phenothiazine; phenylbutazone (Butazolidin); phenindamine tartrate (Thephorin); piperazine anhydrous; piperazine hexahydrate (Antepar); piperazine citrate; potassium fluoride; potassium iodate; potassium iodide; potassium permanganate; polymyxin B sulfate; providone-iodine (PVP-I); procaine HCl; promazine HCl (Sparine); promethazine HCl (Phenergan); quinacrine HCl (Atabrine); quinine hydrochloride; quinine sulfate; quinoline; 12 resorcinol compounds as follows: resorcinol; 4-amylresorcinol; 4-butylresorcinol; 4-ethylresorcinol; 4-isoamylresorcinol; 4-isobutylresorcinol; 4-heptanoylresorcinol; 4-propionylresorcinol; 4-propylresorcinol; 4-tetradecylresorcinol; 4-undecylresorcinol; 4-valerylresorcinol; silver nitrate; sodium acetrizoate (Urokon sodium); sodium antimony biscatechol (Fuadin); sodium iodide; sodium lauryl sulfate; sodium perborate; sodium thioglycollate; 1,2-stearal glyceryl disodium phosphate; stilbamidine; streptokinase-streptodornase; streptomycin; strontium bromide; sulfacetamide sodium; synnematin-B; "Syntha"; tetracycline; tetrahydrofurfuryl nicotinic acid ester (Trafuril); tetramethyl thiuram disulfide (TMTD); thiomethylenephosphoramide; thorium dioxide; triethylenemelamine (TEM); triethylenethiophosphoramide; tripelennamine HCl (Pyribenzamine); trypsin; urea; "Vel"; zinc chloride.

In Vivo Investigation of Chemicals.

Using the method described by Larsh and Kent,[9] in their studies of *Trichinella spiralis*, 24 mice were each subjected to gastric instillation of 200 larvae of *A. caninum*. One, 3, and 5 days later, 6 mice were each given 1.0 mg. neoarsphenamine intravenously; 6 mice were given 0.1 mg. sodium antimony biscatechol (Fuadin) intramuscularly; 6 mice were given 0.1 mg. bismuth sodium p-aminophenylarsonate (Arseno-bismulate) intramuscularly; and 6 mice were untreated. All animals receiving sodium p-aminophenylarsonate died before completion of the study. The others were sacrificed 7 days after infection (2 days after completion of exposure to the medicaments) and after skinning and evisceration were digested in a solution of 1.0% HCl and 0.7% pepsin. Subsequently osseous material was strained off and the soft tissue digestant examined *in toto* for living larvae. Those mice receiving neoarsphenamine yielded an average of 57% recovery of viable larvae; in those receiving sodium antimony biscatechol the recovery rate was 56%; while the controls showed 69% of the original 200 larvae could be identified as viable.

In Vitro Investigation of Physical Agents.

(A) *High Temperature.* Suspensions of larvae in test tubes containing tap water when immersed in a water bath at 48°C. (118.4°F.) were repeatedly rendered permanently immobile in 15 minutes. However, exposure to 46°C. (114.8°F.) and 44°C. (111.2°F.) for as long as 22 minutes and 44 minutes, respectively, failed to immobilize them.

These figures are comparable with other data available on the hyperthermal death point of human hookworm larvae. According to Belding[10] they die in less than 40 minutes at 45°C. (113°F.).

(B) *Low Temperature.* On several occasions in the same type of well slide used in the chemical experiments, a suspension of approximately 30 larvae were placed in a 6% aqueous gelatin solution and frozen with ethyl chloride or dichloro-tetra-fluoro-ethane (Freon) to complete solidification for periods of 5 minutes. Upon thawing the larvae immediately regained complete activity and upon microscopic examination showed no evidence of damage. The temperature attained in these experiments was (-)23°C. (-9.4°F.).

Employing a "deep freeze" (–)10°C. (14°F.), larvae were subjected to long-term refrigeration in a 6% aqueous gelatin solution. A majority of them were quite viable at the end of one week.

(C) *Ionizing Radiation.* The effect of x-radiation on larvae was investigated as follows: approximately 100 larvae were suspended in 8 drops of water in well slides and subjected to dosages of x-rays of 1,000 r. at 16 cm., 5,000 r., 8,000 r., and 12,000 r. at 8 cm.; and 25,000 r. and 50,000 r. at 4 cm. distance (60 kv., 20 ma., 1 mm. Al. filtration, H.V.L.=1.02 Al.). Following irradiation these preparations were sealed with a cover slip. Within the observation period of one week no decrease in motility of either the irradiated larvae or the controls could be detected. Controls consisted of larvae of the same hatching prepared as above but not subjected to irradiation.

The same types of preparations were subjected to irradiation from a radium plaque in contact (5 mg. Ra. 0.1 mm. monel filter) for 72 hours, following which the irradiated larvae and the controls were observed for 12 days. A majority (and equal) number of them remained actively motile.

In Vitro Investigation for the Presence of Antibodies.

Several preparations consisting of a suspension of approximately 10 active larvae in 0.6 ml. serum obtained from dogs known to have a natural infection of *A. caninum,* were placed in well slides and observed. Within 10 hours there appeared a granular precipitate which agglutinated about the cuticle of the larvae with heaviest concentration in the regions of the oral and excretory pores (Fig. 2). This phenomenon increased until the larvae were completely entangled in the mass of these particles and their whip-like motion gradually stilled, a process generally requiring 3 to 4 days. Continued observation lead to the belief that these larvae were dead.

Similar preparations of larvae suspended in serum obtained from animals not subject to infection with *A. caninum* (e.g., rabbit, guinea pig) failed to produce this phenomenon.

Employing human serum from a limited number of patients with and without evidence of creeping eruption in the same fashion as above, inconsistent results in regard to the formation of a precipitate were obtained. These results are presented in table 3.

FIG. 2

Moderately advanced precipitation around larvae suspended in serum from a dog with natural infection with *A. caninum.*

TABLE 3

Case #	*Duration of Eruption (Days)*	*Number of Larvae*	*Degree of Precipitation*
1	21	"shoulder, flank, legs"	+
2	2	"arms, flank, thighs, abdomen"	+
3	14	"generalized"	—
4	2	?	±
5	?	?	+
6	33	1	±
7	36	10	++
8	50	"hundreds"	—
9 (infant)		CONTROLS	—
10		no history or presence of creeping eruption	++
11			±

Estimated degree of precipitation in human sera when exposed to larvae of *A. caninum.* No correlation between severity or duration of infection and precipitation can be demonstrated here.

Comment

The methods used in these studies designed to discover chemicals which might be toxic for *A. caninum* are crude at best. It is to be hoped they are not misleading. At least our results closely parallel the pioneer *in vitro* studies of Ritchie and King[6] and the very recent similar investigations of Blank, Winter and Beck.[7] The concentrations used by Ritchie and King[6] were in general greater than those employed by us, while those used by Blank, Winter and Beck[7] were broader than ours, but roughly they were within the range reported here. Our efforts were largely directed to repeating the work done by Ritchie and King and to extend the list of compounds tested. Though time-wise our studies were not as precise as theirs, we confirm a definite action of hexylresorcinol as shown by Ritchie and King and suggest a few more compounds which seem to show promise. While the studies of Blank and his colleagues concerned many newer compounds, especially several organic phosphates, there was some overlapping between their investigations and ours. They found "Co-ral," malathion, Dilan, chlorpromazine, and Vapam held promise as larvacides. These compounds were not tested by us. However, we did examine the organic phosphates, Parathion, thiomethylenephosphoramide, and triethylenethiophosphoramide and found them without toxic activity by our methods of study.

Refinements which conceivably could be valuable would be the adjustment of pH to approximate that of human tissue and the use of molar dilutions rather than those based on volume or weight percentages. Although it is known that *Ancylostoma* larvae are quite insensitive to pH change (Von Brand[8]), developing as they do from pH 4.0 to pH 10.0, the activity of a chemical on the parasite might be altered in this large range of hydrogen ion concentration. While we agree with Levine and Ivens[11] that an expression of dilution in moles rather than percentage of weight or volume is more exact, we do not feel that in this type of crude screening study such precision is necessary.

Accepting the methods used here for *in vitro* testing as the best presently available, it is evident that our results hold little promise for an improved treatment of creeping eruption. A total of 157 chemicals were screened and only 4 found which killed the larvae within one hour (Group I). These were 4-n-hexylresorcinol, 4-isohexylresorcinol, iodine (elemental), and pyridine. Chemicals which killed the larvae within 12 hours were n-decyl-, heptyl-, and octyl-4- substituted resorcinols and iodoacetate sodium (Group II).

The action of iodine is quite striking, and perhaps chemicals containing this element deserve further study. The action of iodoacetate sodium lends some support to this idea. However, sodium and potassium iodide are innocuous as is the high molecular polymer povidone-iodine. A similar case may be made for pyridine and the hexylresorcinols, particularly since certain drugs containing these chemical configurations are used medicinally. The forms in which these "promising" chemicals were employed in these experiments are of course intolerable to humans by systemic administration.

The largely negative results of these experiments attest the larva's high degree of independence of its environment. This may be explained by the imperviousness of the cuticle, the nonfunctioning state of the mouth parts in the infective filariform stage, and the apparent absence of exogenous metabolic requirements. We have maintained larvae with full motility in sterile distilled water for more than 60 days.

One might reasonably postulate that while a chemical may not be larvacidal *in vitro,* its degradation products *in vivo* could be noxious to the organism. Therefore, studies of the survival rate of the larvae in the soft tissues of mice after administration of an arsenical, an antimonial and a bismuth-arsenical preparation were considered appropriate. Those animals receiving the bismuth-arsenical preparation were of no value because they died before completion of the study.

In the 6 mice receiving neoarsphenamine, and the 6 receiving sodium antimony biscatechol following infection with 200 larvae each, the recovery rate of living organisms was 57% and 56%, respectively, while in the untreated controls 69% were recovered. This is not considered a significant difference and would indicate that with this method of study, definite toxicity of these drugs for the larva is not demonstrated.

This technic, however, lends itself well to the *in vivo* investigation of *Ancylostoma* larvae and perhaps will find favor with other investigators of this general problem.

Our experiments with high temperatures lethal to the larva were in agreement with those of Belding[10] inasmuch as we were able to demonstrate that the parasites were killed *in vitro* at a temperature of 48°C. (118.4°F.) sustained for a period of 15 minutes. Lower temperature or less exposure was not lethal. It would appear that such a procedure might be clinically applicable, since we demonstrated that a water bath temperature of 48°C. (118.4°F.) is tolerable to humans on the extremities. However, in two patients with creeping eruption of the foot, immersion in a water bath for 15 minutes at 48°C. (118.4°F.) to 50°C. (122.0°F.) failed to kill the larvae. Such temperature is not damaging but is subjectively just on the border of tolerance. Perhaps circulatory conduction of heat away from the involved region sets up a situation which does not parallel the *in vitro* observations.

The time-honored freezing technic, when subjected to experimental examination, bears out the contention of dermatologists with most experience in this disease. That is, that the blistering and exfoliation, not the low temperature, are effective treatments. We have demonstrated that as chemicals neither dichloro-tetrafluoro-ethane nor ethyl chloride are lethal for the larvae. The fact that the larvae are quite viable after being subjected to a temperature of (–)23°C. (–9.4°F.) for 5 minutes *in vitro* demonstrates that low temperature in itself is not lethal. Long-term refrigeration by the methods used here were also innocuous. This is not in agreement with the findings of Furuyama quoted by Belding[10] who found that human hookworm larvae were killed in less than 24 hours at (–)10°C. (14.0°F.) to (–)12°C. (10.4°F.).

The experimental exposure of larvae to irradiation by both x-ray and radium was explored only because in the regions where creeping eruption is common there are occasional rumors of "cures" by x-ray therapy. Some formal support was given to this idea by the publication of Vassallo[12] in 1939. It was not unexpected that we found that ionizing radiation, even in dosage incompatible with survival of normal human cells, was not lethal to larvae. The ultimate effect of such radiation on the development and progeny of these larvae was not explored since it has no relation to the treatment of human creeping eruption. However, it is evident that such radiation *per se,* even in enormous amounts, has no immediate deleterious effects on the parasite.

The production of a substance in the serum of animals suffering natural infection with *Ancylostoma* which will lead to the formation of a precipitate about the body of the larva has been previously described by Otto.[13] This phenomenon we have repeatedly demonstrated using the serum of dogs known to have a heavy natural infection of *A. caninum.* In like manner, its absence was demonstrated when using serum of animals assumed to be immune to infection with this parasite. It should be emphasized that the maximum production of this precipitate is a slow process generally requiring 3 to 4 days, but its appearance is inevitable and lethal. The question of the applicability of this phenomenon to human creeping eruption remains entirely unanswered. Through the courtesy of several dermatologists in Florida (Farrington, Sompayrac, Bowen, Blank), serum of a small number of patients with both mild and severe creeping eruption was obtained and compared with serum from persons with minor infections and those assumed to have had no contact with *A. caninum.* This survey fails to establish the premise that a heavy infection of the human with *Ancylostoma* for a considerable period of time, e.g., Case 8, must necessarily lead to the formation of demonstrable antilarval precipitation. However, a possible explanation for this case might be that an excessive amount of antigen submerged the antibody level, producing an anergic state. On the other hand, the serum of certain individuals, with or without known exposure to *A. caninum,* is completely devoid of this precipitating factor. All in all, in the few patients studied here, no correlation between current infection with *A. caninum* (or *A. braziliense*) larvae and the presence of precipitating substances in the serum could be made. However, one must also take into account that some of the patients may have had a previous encounter with these organisms,

or are currently harboring other intestinal helminths with similar antigenic properties. We have been unable to pursue further this investigation of antibody production, though the subject offers considerable fascination. Perhaps others, especialy in regions where extensive infections are frequently encountered, may find it an attractive field of endeavor.

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HOTEL RESERVATION APPLICATION FORM

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APPEARS IN THIS ISSUE

MAKE YOUR RESERVATIONS EARLY!

Primary Hypercholesteremia and Idiopathic Hyperlipemia: Clinical, Biochemical and Therapeutic Considerations*

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More and more interest is developing in these two disturbances in lipid metabolism, not only because of local cutaneous lesions but because of the systemic implications. The author has nicely differentiated the two entities on clinical and biochemical grounds.

Two diseases are recognized in which for no apparent reason a great increase in the amounts of serum lipids is found. They are primary hypercholesteremia and idiopathic hyperlipemia. In primary hypercholesteremia there exists an increase in the serum cholesterol and phospholipids. On the other hand, in idiopathic hyperlipemia one finds not only an increase in serum cholesterol and phospholipids but also an increase in the amount of neutral fat in the serum. This increase in neutral fat causes a milky appearance of the fasting serum. Since in primary hypercholesteremia the serum is clear, it is possible to differentiate these 2 diseases simply by inspection of the serum. It is important that such simple differentiation between these 2 diseases is possible because the 2 diseases can greatly resemble each other clinically inasmuch as both may show tuberous xanthomas and xanthomas of the tendons.

The clinical manifestations will be discussed first, then the biochemical findings and the etiology, and finally the treatment of primary hypercholesteremia and idiopathic hyperlipemia.

Clinical Manifestations

Primary Hypercholesteremia. Primary hypercholesteremia may remain asymptomatic throughout life, but in many patients clinical manifestations develop during middle and later life. If the hypercholesteremia is severe, clinical manifestations may begin even in early childhood.

Among the cutaneous manifestations xanthelasmas of the eyelids are most common (Fig. 1). Usually they do not appear before the age of thirty. It should be emphasized, however, that the presence of xanthelasmas alone does not justify a diagnosis of primary hypercholesteremic xanthomatosis because xanthelasmas can occur without evidence of hypercholesteremia, especially in elderly people.

Tuberous xanthomas are occasionally encountered in primary hypercholesteremia. However, they are more common in idiopathic hyperlipemia than in primary hypercholesteremia.[1] They can attain a size of several centimeters in diameter and show, once they have formed, little tendency to involution. One finds them most commonly on the elbows and knees, but occasionally also on the hands and feet as well as elsewhere on the extremities and on the buttocks.

Tendon xanthomas are common in primary hypercholesteremia and occur especially on the Achilles and patellar tendons and also on the extensor tendons of the fingers and on the triceps tendons near the olecranon. Because tendon xanthomas are often small they can easily be overlooked.

The frequent occurrence of coronary sclerosis gives primary hypercholesteremia a serious prognosis. More than half of the patients develop coronary heart disease. The coronary heart disease can begin at an early age and often leads in middle age, and occasionally even at a youthful age, to death. As a matter of fact, if a patient dies of coro-

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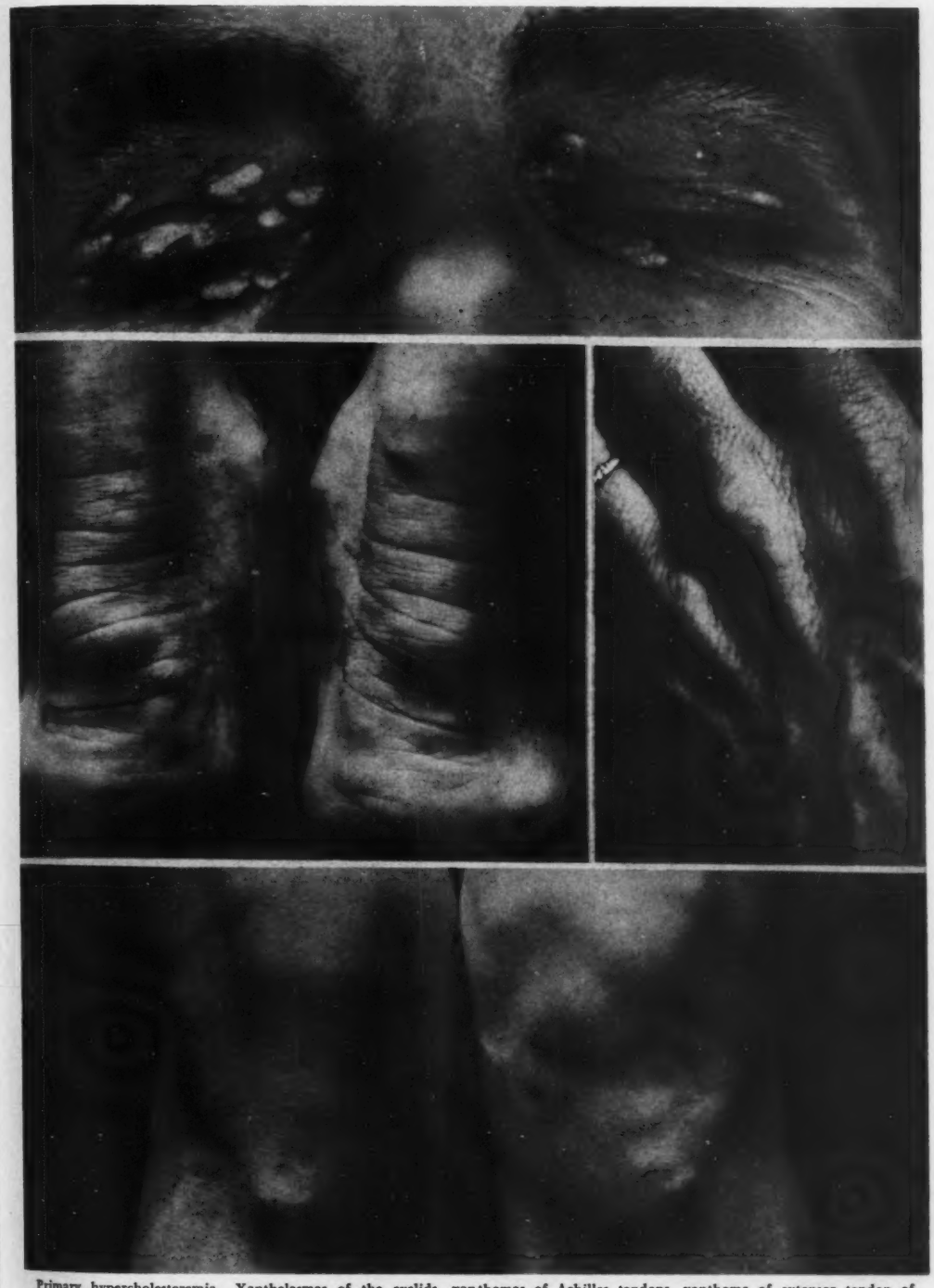
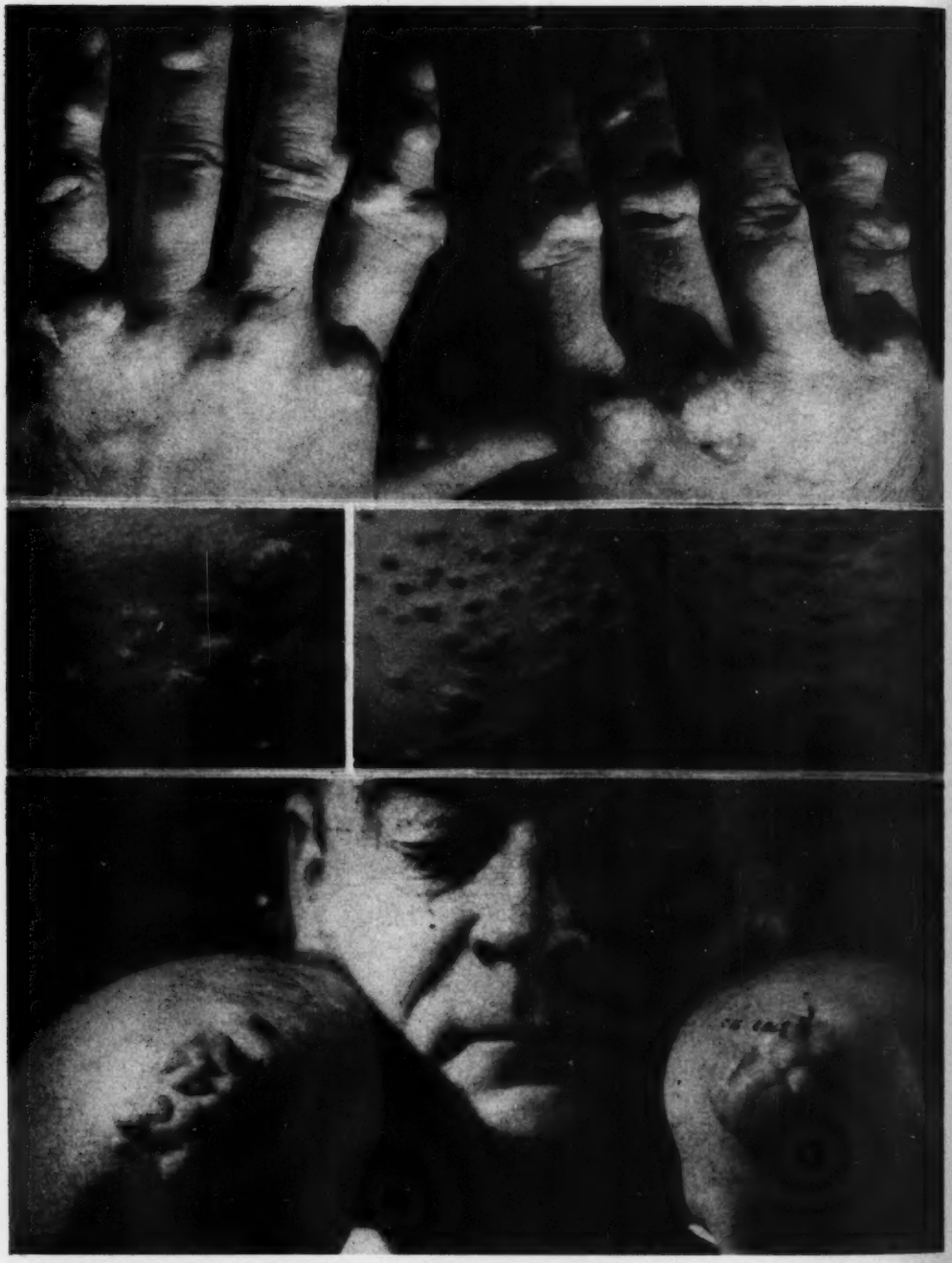
FIG. 1



Primary hypercholesteremia. Xanthelasmas of the eyelids, xanthomas of Achilles tendons, xanthoma of extensor tendon of middle finger and xanthomas of patellar tendons.

FIG. 2



Idiopathic hyperlipemia. Tuberous xanthomas of the hands, eruptive xanthomas on knee and buttocks and tuberous xanthomas on elbows. Note the absence of xanthelasmas of eyelids.

nary heart disease at an early age one can assume that the patient had primary hypercholesteremia.[2]

Primary hypercholesteremia is a dominantly inherited disease. The patient can therefore expect that half of his offspring will inherit the disease with its poor prognosis.

Idiopathic Hyperlipemia. In idiopathic hyperlipemia, as in primary hypercholesteremia, clinical manifestations may be lacking. Such cases usually are found on routine blood examinations because of the turbidity of the serum. Two types of cutaneous xanthomas may occur: tuberous xanthomas and eruptive, papular xanthomas.[1] The large tuberous xanthomas occur most commonly on the elbows and knees but also on the hands and feet as well as in other locations (Fig. 2). The small eruptive, papular xanthomas come and go with the fluctuation of the serum lipid levels. They can occur anywhere on the skin, but are found most commonly on the buttocks and on the posterior aspects of the thighs. Xanthelasmas of the eyelids, which are common in primary hypercholesteremia, hardly ever occur in idiopathic hyperlipemia. Tendon xanthomas occur occasionally but less often than in primary hypercholesteremia.

Attacks of abdominal pain are quite common. They may present a diagnostic problem in patients of whom it is not know that they have idiopathic hyperlipemia. Not infrequently the acute abdominal pain then leads to an unnecessary operation. It is probable that a pancreatitis is the cause of the abdominal pain. This is suggested by the fact that on several occasions exploratory laparotomy revealed a pancreatitis. Furthermore, in several patients an elevation of the amylase level was found in the serum or an increased excretion of amylase in the urine. It is not fully decided as yet if the pancreatitis represents in all instances a consequence of the idiopathic hyperlipemia or, if in some cases, the pancreatitis is the primary disease producing the hyperlipemia. The following facts, however, favor the view that the pancreatitis is the consequence rather than the cause of the hyperlipemia:[3] first, in several patients the existence of the hyperlipemia preceded the onset of abdominal pains; second, several patients stated that they had xanthomas before they had abdominal pains; third, one patient reported in the literature[4] still had hyperlipemia 8 years after his last attack of abdominal pain; and fourth, several patients with pancreatitis and hyperlipemia had relatives with asymptomatic hyperlipemia.

An additional, not infrequent finding in idiopathic hyperlipemia is enlargement of the liver and spleen. A diet low in fat frequently causes a decrease in the size of the liver and spleen in such patients.

Coronary heart disease may occur in association with idiopathic hyperlipemia. Although a few instances of death due to coronary heart disease have been reported, coronary heart disease is neither as common nor generally as severe as in primary hypercholesteremia, so the prognosis as to life is more favorable in idiopathic hyperlipemia than in primary hypercholesteremia.[1]

A familial occurrence of idiopathic hyperlipemia has been occasionally observed, especially among siblings. It has been assumed, therefore, that idiopathic hyperlipemia in some instances is recessively inherited.[5]

Comparison of the Clinical Findings of Primary Hypercholesteremia and Idiopathic Hyperlipemia (Table 1). If one compares the clinical findings of primary hypercholesteremia and idiopathic hyperlipemia one finds that xanthelasmas occur frequently in hypercholesteremia but very rarely in hyperlipemia. On the other hand, papular eruptive xanthomas and abdominal cramps occur only in idiopathic hyperlipemia. Tuberous xanthomas, tendon xanthomas and coronary heart disease can occur in both diseases, although tuberous xanthomas are more common in hyperlipemia, and tendon xanthomas and coronary heart disease are more common in hypercholesteremia. A familial history of the disease is regularly observed in hypercholesteremia, which is dominantly inherited,

TABLE 1

	Primary Hypercholesteremia	*Idiopathic Hyperlipemia*
Xanthelasmas	+ + +	(+)
Eruptive xanthomas	—	+ + +
Abdominal pain	—	+
Tuberous xanthomas	+	+ +
Tendon xanthomas	+ + +	+
Coronary heart disease	+ + +	+
Familial history	+ + +	+

Comparison of the clinical features of primary hypercholesteremia and idiopathic hyperlipemia.

and only rarely in hyperlipemia, which often is not an inherited disease and occasionally recessively inherited.

Biochemical Findings

1. *Analysis of Serum Lipids.*

Primary Hypercholesteremia. Chemical analysis of the serum lipids in primary hypercholesteremia reveals an elevation of the values for cholesterol and phospholipids. The degree of elevation is quite constant and major spontaneous fluctuation, as in idiopathic hyperlipemia, do not occur. As a rule, the elevations of the cholesterol and phospholipids are only moderate so that values of cholesterol in excess of 600 mg. per 100 ml. of serum are only rarely encountered. The amount of neutral fat is normal and, therefore, the serum is clear in the fasting state.

Idiopathic Hyperlipemia. In idiopathic hyperlipemia one finds a moderate to marked elevation of the values for serum cholesterol and phospholipids. The average values for cholesterol and the phospholipids lie higher in idiopathic hyperlipemia than in primary hypercholesteremia so that cholesterol values in excess of 1,000 mg. per 100 ml. of serum are not unusual.[1] The level of neutral fat can reach several thousand milligrams. The serum has a milky appearance except when the hyperlipemia is in remission. A fairly good correlation exists between the degree of turbidity of the serum and the amount of neutral fat it contains. Thus, inspection of the serum or optical determination of the degree of its turbidity gives quite good information about the degree of hyperlipemia. Considerable spontaneous fluctuations of the lipid values can occur in the course of weeks and months. Still greater fluctuations take place under the influence of diet in that a diet low in fat often brings about considerable reductions of the lipid values.

Injections of heparin also bring about a marked reduction of the lipid values in idiopathic hyperlipemia. A single intravenous injection of 100 mg. of heparin usually produces within one hour, and in some patients even within 15 minutes, a considerable reduction of the values for neutral fat, cholesterol and phospholipids, amounting to several hundred milligrams per 100 ml. of serum.[6] This is in contrast to primary hypercholesteremia in which heparin causes only a very slight decrease in the lipid values.

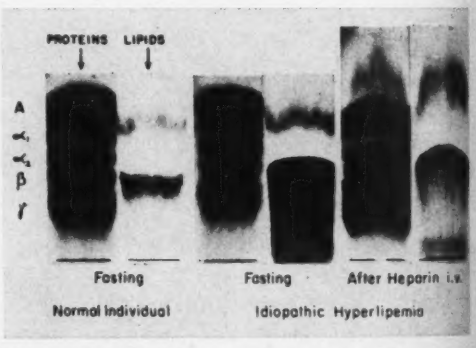
2. *Electrophoretic Analysis.*

Primary Hypercholesteremia. Electrophorectic analysis of the serum proteins by means of paper electrophoresis reveals in primary hypercholesteremia, on paper strips stained for lipids, a normal amount of alpha lipoproteins and a moderately increased amount of beta lipoproteins.[7]

Idiopathic Hyperlipemia. In idiopathic hyperlipemia the amount of beta lipoproteins is also increased, often considerably. In addition, a heavily staining trail extends from the beta lipoprotein band to the starting line of the electrophoretic migration (Fig. 3). This trail represents the chylomicra of neutral fat.

The effect of an intravenous injection of heparin is interesting. No effect is noted on the electrophoretic pattern of a normal fasting serum. However, in idiopathic hyperlipemia one observes an increase in the speed of migration of both the alpha and beta lipoproteins so the beta lipoproteins migrate with the speed of alpha-1 globulin and the alpha lipoproteins migrate faster even than albumin as the so-called pre-albumin component.[7] One also notes a decrease in the intensity of staining of the trail of chylomicra

FIG. 3



Paper electrophoretic patterns. In each of the 3 patterns, the left strip is stained for proteins and the right strip for lipids. The left pattern is obtained in a normal individual.—The pattern in the middle is obtained in a patient with idiopathic hyperlipemia; the amount of beta lipoproteins is also increased. In addition, a heavily staining trail, representing the chylomicra, extends from the beta lipoproteins to the starting line. —The right pattern is obtained in the same patient with idiopathic hyperlipemia 15 minutes after an intravenous injection of 100 mg. of heparin. The trail of chylomicrons shows much less intensity of staining than before the injection. The beta lipoprotein band has increased its electrophoretic mobility so that it moves with the speed of alpha-1 globulin; and the alpha lipoprotein band moves faster than albumin as pre-albumin component (P.A.).

because of a decrease in the number and size of the chylomicra.

3. *Ultracentrifugal Analysis.*

Primary Hypercholesteremia. Ultracentrifugal analysis of the serum beta lipoproteins by means of flotation reveals in normal serum nearly all the beta lipoproteins in the lowest S_f class, S_f 1-10 (the class with the lowest flotation rate). Only small amounts are present in the next higher S_f class, S_f 12-20 (Fig. 4).

In primary hypercholesteremia the ultracentrifugal pattern shows, commensurate to the increase in the amount of serum cholesterol and phospholipids, an elevation of the beta lipoproteins in the lowest S_f class, S_f 1-10. Occasionally, one finds, in addition, an elevation of the beta lipoproteins in the next higher S_f class, S_f 12-20. We found among 7 patients with primary hypercholesteremia, all of whom had xanthomas, 4 patients with normal amounts of beta lipoproteins in the S_f 12-20 class, 2 patients with a slight elevation and 1 patient with a moderate elevation.[8] Wheeler and Sprague[9] found among 22 patients with primary hypercholesteremia only 3 patients with an elevation of the beta lipoproteins in the S_f 12-20 class. On the other hand, Gofman and associates[10] regard a slight to moderate elevation of the beta lipoproteins in the S_f 12-20 class as a regular feature of hypercholesteremia. Gofman and his associates regard this group of beta lipoproteins as highly significant, because an increase in the S_f 12-20 class is, in their experience, frequently associated with coronary atherosclerosis. They have even spoken of an atherosclerotic index on the basis of which Gofman claims the development of coronary atherosclerosis can be predicted. Although his claim may be accepted if one averages a large number of patients, one cannot accept his claim as an evaluation or a prognosis for individuals.

Idiopathic Hyperlipemia. In contrast to primary hypercholesteremia, in which ultracentrifugal analysis of the beta lipoproteins reveals only slight deviations from normal, one finds in idiopathic hyperlipemia a grossly abnormal ultracentrifugal pattern.[8] One finds a great increase in the high S_f classes, S_f 30-70 and S_f 100-400, of which normal fasting serum and the serum of patients with primary hypercholesteremia contains only small amounts. This great increase in the high S_f classes can be explained by the large amounts of lipoproteins containing neutral fat. Such lipoproteins have, because of the low density of neutral fat, a high flotation rate. The amount of beta lipoproteins in the S_f 12-20 class usually is moderately increased. On the other hand, their amount in the S_f 1-10 class, which normally contains most of the beta lipoproteins, is greatly decreased.

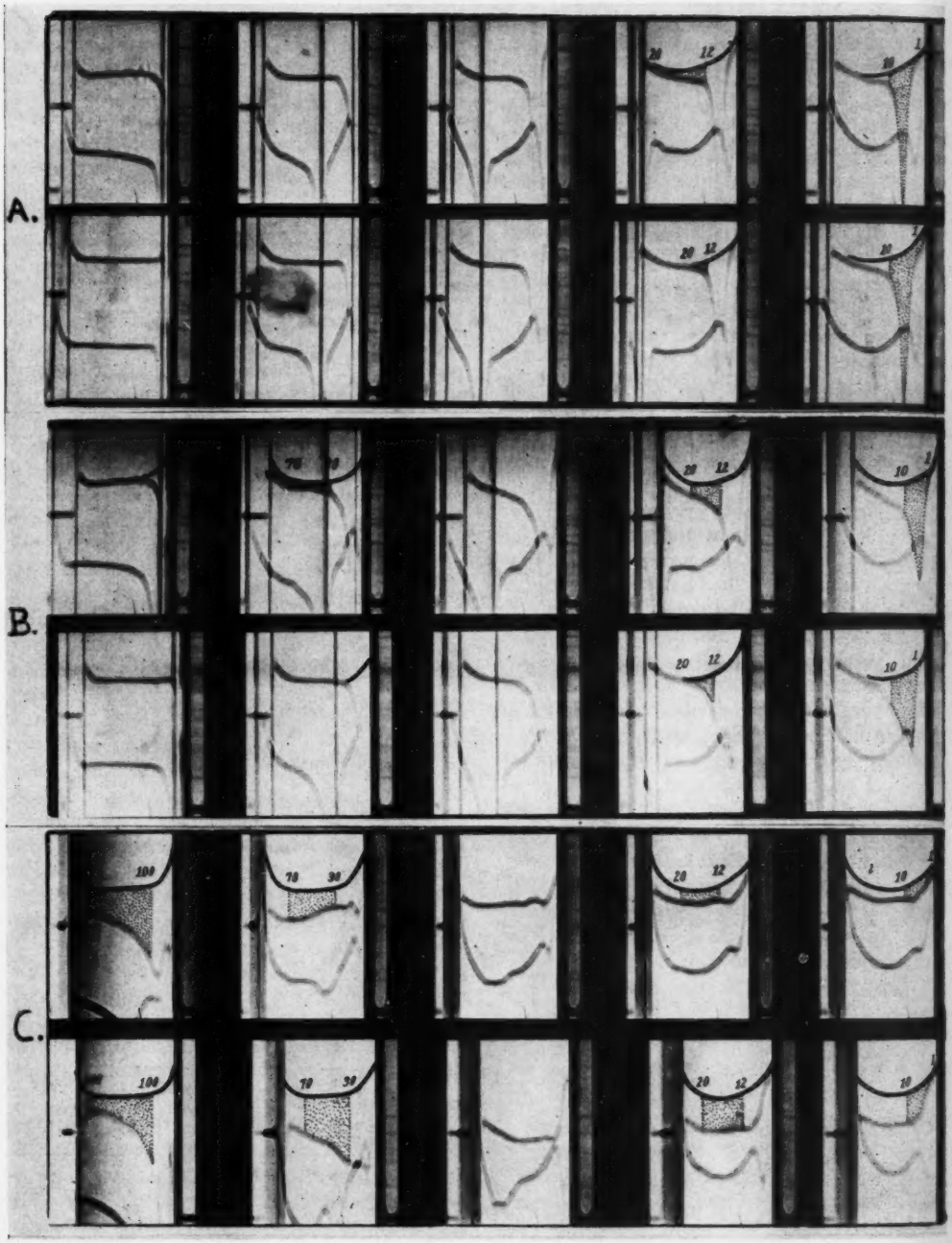
An intravenous injection of heparin has only a slight effect on the ultracentrifugal pattern of normal individuals and of patients with primary hypercholesteremia since the lipoproteins are already congregated in the low S_f classes. In idiopathic hyperlipemia, however, an intravenous injection of heparin causes considerable changes[8] because of a shift of the beta lipoproteins from the higher to the lower S_f classes, from the S_f 100-400 class to the S_f classes 30-70, 12-20 and 1-10 (Fig. 4). Heparin, by accelerating the physiologic process of converting beta lipoproteins of the higher to the lower S_f classes, thus causes in idiopathic hyperlipemia a change in the ultracentrifugal pattern towards a more normal appearance.

Cause of Hyperlipemia

Our investigations have so far not led to any conclusions as to the cause of primary hypercholesteremia. On the other hand, the marked effects of a low fat diet and of heparin on the serum lipid levels in idiopathic hyperlipemia—in contrast to primary hypercholesteremia where such effects are lacking—suggested a delayed elimination of the lipids from the blood stream. To test this hypothesis we have carried out experiments which established the presence of an inhibitor of the clearing factor enzyme in the blood serum of patients with idiopathic hyperlipemia.

Infusions of Fat Emulsions. In order to determine whether or not a delayed elimination of lipids existed in patients with idiopathic hyperlipemia, we gave 9 patients with idiopathic hyperlipemia, 4 patients with primary hypercholesteremia and 14 control persons an intravenous infusion of 500 ml. of a 10% cottonseed oil emulsion.[11] In 13 of the 14 control persons and in the 4 patients with primary hypercholesteremia we found

FIG. 4

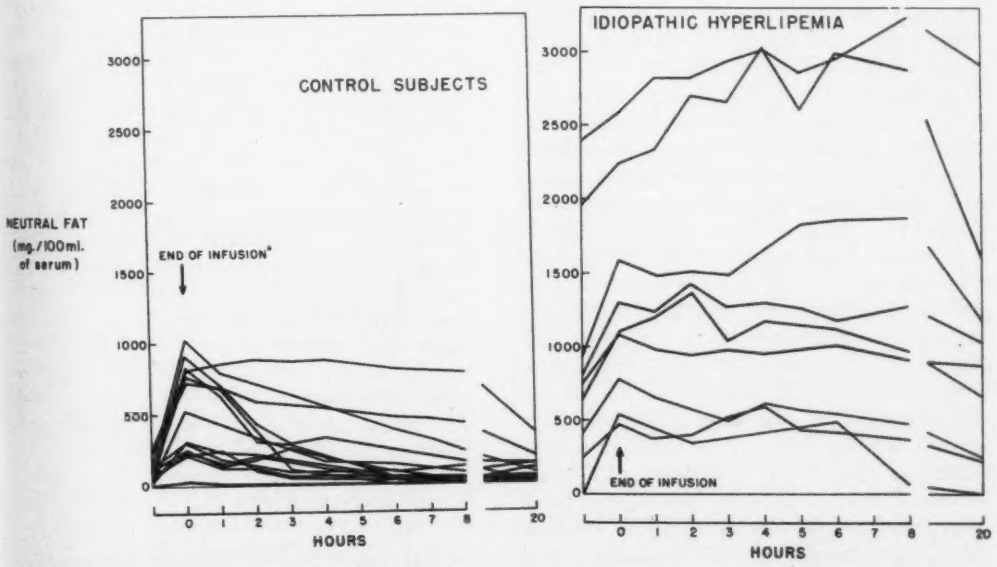


Ultracentrifugal patterns. In each of the 3 patterns the upper row represents the pattern before an injection of heparin and the lower row represents the pattern 60 minutes after the intravenous injection of 100 mg. of heparin. The upper pattern (A) is obtained in normal subject. Most of the lipoproteins are present in the lowest S_f class, S_f 1-10. —The pattern in the middle (B) is obtained in a patient with primary hypercholesteremia. A small amount of the lipoproteins is present in the S_f 30-70 class and the amounts in the S_f 12-20 and S_f 1-10 are increased. —The lower pattern (C) is obtained in a patient with idiopathic hyperlipemia. Very large amounts of lipoproteins are present in the S_f 100-400 and S_f 30-70 classes. After an injection of heparin a shift of lipoproteins has occurred from the highest S_f class to the lower S_f classes.

that the values for neutral fat, which had increased as a result of the infusion, usually returned to the approximate starting level within 6 hours (Fig. 5). On the other hand, of the 9 patients with idiopathic hyperlipemia only one patient, in whom the hyperlipemia was in full remission, showed a normal elimination of fat from the blood stream. In the other 8 patients no decrease in the values for neutral fat took place during the first 6 to 8 hours after the fat infusion. In the 5 patients with the most pronounced hyperlipemia we found that the values for neutral fat during the first few hours after the infusion even rose above the level exisiting at the end of the infusion. The slow disappearance of the infused fat in our patients with idiopathic hyperlipemia strengthened the thesis that a delayed elimination of lipids from the blood stream exists in idiopathic hyperlipemia and suggested a disturbance in the lipemia-clearing mechanism.

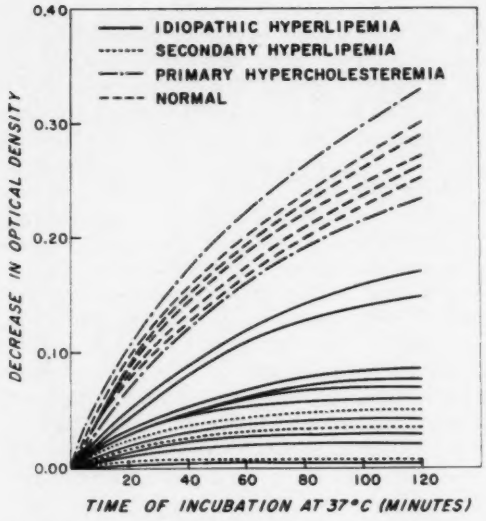
Measurement of Clearing Activity. In order to investigate the possibility of a disturbance in the lipemia-clearing mechanism the following *in vitro* experiments were carried out.[12] We first obtained clearing-factor containing "active" serum by giving normal individuals 100 mg. of heparin intravenously and drawing blood 30 minutes later. We then mixed 0.6 ml. of this "active" serum with 0.6 ml. of fasting serum obtained either from a normal subject or from a patient with primary hypercholesteremia or idiopathic hyperlipemia. To this mixture 0.3 ml. of a standard fat emulsion was added as substrate. As an indication of clearing-factor activity the optical density of this mixture was measured spectrophotometrically at intervals of 10 minutes. It was found that, in the presence of serum from patients with idiopathic hyperlipemia, the clearing activity of the clearing-factor containing "active" serum was inhibited. The decrease in optical density, indicating the degree of clearing, observed after 120 minutes varied for the normal and hypercholesteremic sera between 0.23 and 0.33 units, averaging 0.27 units; whereas the amount of clearing in the mixture containing hyperlipemic serum was significantly less, varying between 0 and 0.17 units and averaging 0.07 units (Fig. 6). Although the degree of inhibition exerted by the serum of hyperlipemic patients varied we found that when sufficient amounts of hyperlipemic serum were added to the clearing-factor containing serum the clearing reaction could be suppressed in every case.

FIG. 5



Disappearance curves for neutral fat obtained after the intravenous infusion of a cottonseed oil emulsion in 14 normal subjects (left) and 9 patients with idiopathic hyperlipemia.

FIG. 6



In vitro clearing activity of mixtures of equal amounts of normal post-heparin serum with either normal fasting serum or serum from patients with primary or secondary hyperlipemia or primary hypercholesteremia.

We also tested the sera of patients who had secondary hyperlipemia either due to glycogen storage disease, nephrosis or diabetes and found that these sera also exerted a strong inhibition on the clearing reaction. These *in vitro* experiments suggest that the inhibition of clearing activity present in hyperlipemic serum interferes also *in vivo* with the physiologic elimination of lipids from the blood stream and thus is responsible for the hyperlipemia.

We have recently begun to characterize the inhibitor of lipemia clearing present in primary and secondary hyperlipemia. After high-speed centrifugation of hyperlipemic serum the inhibitor was localized in the supernatant lipid layer. On the other hand, after the intravenous administration of heparin the inhibitor was located in the clear infranatant fraction.[13] The inhibitor was found to be heat-labile and sensitive to changes in pH.[14] It was further found that the serum of patients with hyperlipemia inhibited *in vitro* not only the clearing activity of the clearing-factor enzyme but inhibited also the clearing activity of pancreatic lipase.[14] This indicates that the inhibition of the lipid metabolism in the serum of patients with hyperlipemia is quite profound.

Treatment

Because of the different pathogenesis of primary hypercholesteremia and idiopathic hyperlipemia considerable differences exist in the response to treatment. In general, results of treatment are good in idiopathic hyperlipemia in which a diet low in fat and injections of heparin are effective and poor in primary hypercholesteremia in which these two measures are of no value.

Primary Hypercholesteremia. The reason that a diet low in neutral fat and cholesterol causes no significant lowering of the serum cholesterol level in primary hypercholesteremia lies in the fact that in normal individuals, and probably also in patients with hypercholesteremia, a decreased intake of cholesterol in the diet leads to an increased synthesis of endogenous cholesterol, especially in the liver. Such a relationship between cholesterol intake and synthesis of cholesterol in the liver has been shown by Tompkins and associates to exist in rats and by Gould and associates in dogs.[15] The administration of heparin is ineffective in primary hypercholesteremia in contrast to idiopathic hyperlipemia, because in primary hypercholesteremia the fat-clearing mechanism in the blood stream is not deranged.

In recent years a number of reports have appeared indicating that a decisive lowering of the serum cholesterol can be brought about by an increased intake of unsaturated fatty acids. Ahrens and his co-workers[16] found that in normal individuals a direct relationship existed between the degree of saturation of the fatty acids taken in with the food and the level of cholesterol in the serum. They found that the oral administration of peanut oil, cottonseed oil, corn oil and safflower oil caused a lowering of the cholesterol. They recommended in patients with hypercholesteremia a diet containing less than 25 Gm. of animal fat and, in addition, at least 3 times daily one ounce of corn oil or safflower oil. Lately, it has become customary to give, in place of corn oil or safflower oil, capsules containing unsaturated fatty acids, such as Lenic capsules (made by Crooks and Barnes Lab.) or Lufa capsules (made by U.S. Vitamin Corp.) both of which usually are given in doses of 9 capsules a day.

The results published so far indicate that a decrease in the serum cholesterol can

usually be attained. A significant decrease can be observed not infrequently in individuals with mild hypercholesteremia who are elderly, obese and have lived on a high animal fat diet and a low intake of unsaturated fatty acids. On the other hand, in patients with considerable hypercholesteremia and xanthomas this regimen has led in our experience, as a rule, to only minor decreases in the values for cholesterol.

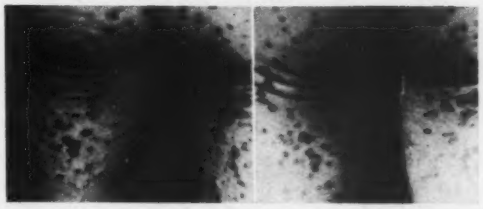
Several other forms of treatment for hypercholesteremia have been under discussion in recent years, such as the treatment with estrogenic substances,[17] sitosterol[18] and nicotinic acid.[19] Although occasional decreases in cholesterol may be observed with any of these 3 forms of therapy, no regular, prolonged, significant decrease in cholesterol can be expected in patients with severe hypercholesteremia and xanthomatosis.

Idiopathic Hyperlipemia. In idiopathic hyperlipemia a diet low in fat is effective because it lessens the strain on the deficient clearing mechanism in the blood serum; and heparin is effective because it stimulates the deficient clearing mechanism.

Treatment with a diet low in fat is particularly effective in those cases in which the lipid values are only moderately elevated. In severe cases, however, even a very strict low-fat diet is of only little help. Probably in such cases the fat clearing reaction in the blood serum is so strongly inhibited that even the lipids entering the blood stream from the fat depots of the body cannot be cleared adequately. In such patients heparin which stimulates the clearing reaction can be of value.

In order to test the effectiveness of heparin as a treatment in idiopathic hyperlipemia, we treated 5 patients with idiopathic hyperlipemia while they were on a normal and not on a low-fat diet.[20] In all 5 patients daily injections of heparin produced an impressive reduction of the lipid values. In the 3 milder cases the lipid values decreased nearly to normal, but in the 2 severe cases with initial values of neutral fat above 3,000 mg. per 100 ml. of serum a decrease to normal could not be attained in spite of the fact that large doses of heparin were given daily for several months. We observed in all 5 cases that as soon as the injections were given every other day instead of daily the lipid values rose again. Of the various forms of treatment which we tested, namely intramuscular injections of an aqueous solution of heparin, intramuscular injections of depot heparin, and intravenous infusions of aqueous heparin for a period of 6 to 8 hours daily, we found the last form the most effective. The best practical approach to the treatment of idiopathic hyperlipemia at present is a low-fat diet to which are added in severe cases occasional courses of heparin, given either as intravenous infusions of aqueous heparin in a hospital or as daily intramuscular injections of depot heparin without hospitalization. Under treatment with diet alone or with diet plus heparin one observes quite rapid clearing of the papular, eruptive xanthomas (Fig. 7). The large tuberous xanthomas, however, usually only decrease in size without disappearing completely, probably because they consist to a large extent of fibrous tissue.

FIG. 7



Idiopathic hyperlipemia. Papular, eruptive xanthomas before and after treatment for 2 months with a diet low in fat.

Conclusions

In conclusion, it may be emphasized again that it is important to distinguish sharply between primary hypercholesteremia and idiopathic hyperlipemia because of the great difference in pathogenesis, prognosis and therapy.

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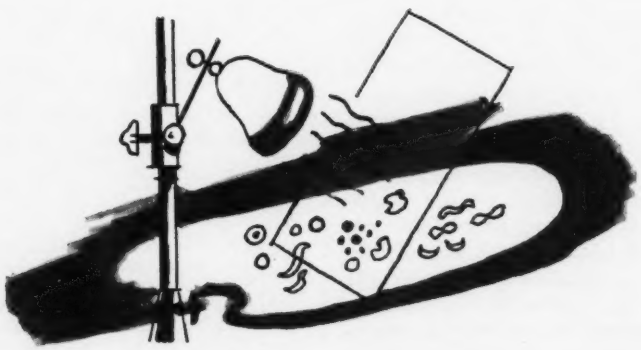


Use of Biperiden Hydrochloride in Parkinson's Disease*

PHILIP F. LERNER, M.D., *Baltimore, Md.*

The use of another of the trihexyphenidyls is reported in disease of the extrapyramidal tract.

WITH THE INCREASING incidence of parkinsonism and of other similar disorders of the extrapyramidal tract, more and more attention has been directed to efforts to alleviate the disabling effects of this illness. Therapy has ranged from the use of simple antispasmodics to major surgery involving destruction of some portion of the extrapyramidal system. So far no drug nor any specific operative procedure has been proved entirely satisfactory. Surgical measures are of recent use, and certainly can be recommended only in a minimal number of selected cases. Therefore, the search for new medicinal agents to provide relief from the spasticity and tremors and the other distressing complaints in those affected with parkinsonism must continue.

Formerly, the most successful drugs have been obtained from the belladonna group, and more recently from derivatives of some histamines and their related compounds. However, many of such agents have, unfortunately, distressing side effects which prevent their use in a significantly large percentage of parkinsonian patients, especially when higher doses are required. Furthermore, after long continued treatment a distinct diminution in effectiveness of the specific medication often occurs, and to control the symptoms adequately, another drug must be added or substituted.

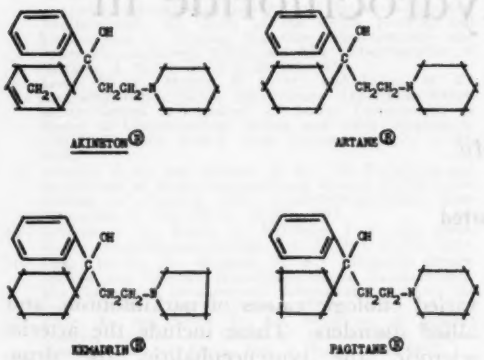
Investigations over the past several years have produced a number of trihexyphenidyls, which have proved to be of value in reducing the intensity of the symptoms and signs of this illness, without excessive annoying side effects. For the past year, we have employed one of these trihexyphenidyls, biperiden HCl, (Akineton) in 36 patients suffering from varied etiologic causes of parkinsonism, and allied disorders. These include the arteriosclerotic, the postencephalitic, the drug-induced, and the so-called idiopathic types, and 5 individuals suffering from severe movement disorders, resulting from hemiballismus (2 cases), and multiple sclerosis (3 cases).

This drug has been used experimentally in Europe for the last 4 to 5 years, with encouraging results in effecting reduction of the disabling features of this syndrome, and with a minimum of the undesirable actions of other medicaments. Clinically, it is 3-piperidino-1 phenyl-1-bicycloheptenyl-propanol-1. It is only slightly soluble in water and alcohol and is stable at normal temperatures. It has a strong nicotinolytic effect, and an anticholinergic action, somewhat less than that of atropine, and a definite myospasmolytic effect. Though it has such an atropine-like action, in producing mydriasis, and in inhibiting salivation, the dose of biperiden necessary to produce dilatation of the pupil in the mouse has been determined to be 6 times that of atropine, and to overcome salivary secretion, induced by pilocarpine, to be 3 times the dose, as compared to atropine. Clinically, biperiden has shown less disturbance of secretory and visual functions, when compared to the drugs of the belladonna group. There has been very little tendency for the occurrence of drowsiness, or disorientation; in one of my cases such reactions occurred, but this patient responded with such symptoms to all of the other trihexyphenidyls, as well as to many other drugs.

Akineton, chemically is akin to trihexyphenidyl HCl (Artane), procyclidine HCl (Kemadrin), and cycrimine HCl (Pagitane), all of which are members of the trihexyphenidyl group. A comparison of their chemical structure appears in figure 1.

*Read before the Section on Neurology and Psychiatry, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

FIG. 1



Results

The 36 patients treated with biperiden HCl were from our private practice and from the clinic and wards of the Mercy Hospital of Baltimore. For the most part, these patients exhibited severe parkinsonian signs and symptoms of fairly long duration, 3 to 20 years; and 8 were of more recent duration, but with considerable movement disorders. Of this latter group, 2 were drug-induced, one an early but severe parkinsonian patient, and 5 were nonparkinsonian illnesses. In these patients who had been on other medications previously, for the most part in combination rather than on any single spasmolytic agent, and on doses high enough to produce distressing and uncomfortable side effects, the addition of biperiden, with the gradual reduction in dosage of some or all of the other drugs, produced effective and satisfactory results, and with an associated reduction in the unpleasant and annoying mydriasis and dryness. The improvement was noted primarily in the symptomatic relief of spasticity and tremor; secondarily, in producing a more normal gait and facial expression; and finally in effecting a more favorable emotional attitude, which paralleled improvement in accomplishing ordinary tasks, such as getting up from a sitting or prone position without marked difficulty, in writing and in coordinating movements.

The 5 cases of nonparkinsonian diseases, showing the severe movement disturbances, responded similarly, although not as rapidly or as intensively. The 2 cases of hemiballismus, both quite severe, had been very poorly controlled on most of the previous spasmolytic medications, and only fairly so on benztropine methanesulfonate (Cogentin) in large doses, but which, however, resulted in definite mental confusion and marked lethargy. The addition of 2 mg. of biperiden 4 times daily, with a reduction in dosage of the methanesulfonate from 8 to 12 mg. to 4 mg. daily, resulted in satisfactory control, so that both patients have been able to carry out normal activities in their own homes. In regard to the 3 individuals suffering from multiple sclerosis, 2 obtained considerable relief from the intense tremors and spasticity, but the third patient, although obtaining similar relief developed gastric irritation which necessitated discontinuance of the biperiden after several trials.

The average dose of biperiden employed in our series in combination with other spasmolytic drugs was 2 mg. 3 to 4 times daily. When used alone, or with minimal amounts of other medicaments, the dosage ranged from 2 to 4 mg. 4 to 5 times daily. It was found possible to reduce in many cases, and to eliminate completely in others, the doses of the other spasmolytic atropine-like agents previously employed, and consequently to decrease considerably the distressing and annoying side effects suffered so often by these patients. Furthermore, it was noted that the moodiness and the hypochondriac or depressive attitude of many of these individuals decreased considerably and fairly rapidly, with the patients becoming more relaxed and calm, and with a concomitant elevation in mood. As with some of the other trihexyphenidyls, there appeared to be a definite associated cerebral stimulating action, resulting in a tendency toward resocialization and interest in activities previously thought impossible or neglected.

Twenty-four of the 36 patients had urine, blood picture, and blood chemical studies with essentially normal results. Side effects, such as excessive dryness of the mouth, vertigo, drowsiness, confusion, and dilatation of pupils were minimal as a rule, and could be reduced with ease upon reduction in dosage. When complaints of gastric irritation occurred (in 5 cases), the addition of an aluminum hydroxide preparation in 4 of the patients, relieved this symptom, so that therapy with the drug could be continued.

In this series, 25 of the 36 patients studied

over a period of 6 to 10 months, showed considerable benefit with this new drug, as manifested by lessening of spasticity and tremors, and in ability to increase their activities and accomplish with more ease many tasks previously accomplished only with considerable difficulty or not at all. No special objective testing for evaluation of effects was done, as Keller[1] and Schwab and Chaefetz[2] had done in judging disturbances in parkinsonism. The opinions of the family and friends, as well as those of the patients themselves, were used for additional assessment values. Seven patients were not benefited and discontinued the drug because of mild annoying side effects.

Summary and Conclusions

Biperiden HCl, a synthetic drug belonging to the trihexyphenidyl group, was employed alone and in combination with other medications in 31 cases of parkinsonism of various etiologic forms and 5 cases of other disorders of movement, with gratifying results, with minimal annoying side effects, and no apparent effects on blood picture and urinary function.

Improvement was noted in reduction of spasticity and tremor, in producing a more normal gait and facial expression, in elevating mood and alertness, and in increasing ability and interest in accomplishment of ordinary activities. The dosage is individualized but averages 2-4 mg. 4 times a day. The therapeutic effects are similar to those of the other drugs of this chemical group but with less distressing side reactions. It must be stressed that biperiden HCl is no absolute cure for parkinsonism, and no treatment is as yet entirely satisfactory in controlling this disabling disease, though this new medication deserves a favorable place in the resources of the physicians in the drug treatment of Parkinson's disease.

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Radioactive Fat Tolerance Studies in Coronary Artery Disease*

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Philadelphia, Pa.

The information which is being gained by the new tool of radioactive fat is of interest and will offer data which will be of practical value in clinical medicine.

DURING RECENT TIMES, there has been an increasing amount of data obtained which implicates a disturbance in lipid metabolism in the genesis of atherosclerosis, especially coronary artery disease. Thus, elevated concentrations of various of the blood lipid fractions, alterations in the ratio of others, and abnormalities in the clearing of alimentary lipemia have been found in many patients with atherosclerosis of the coronary arteries.

However, the technical difficulties involved with most of the procedures used in such studies has been a serious limiting factor in the futherance of our knowledge in this field.

Recently, an oral radioactive fat preparation has become available for this type of experimentation which is proving to be a most valuable metabolic tool. The material is obtained in the form of the triglyceride of oleic acid, an unsaturated fatty acid containing 18 carbon atoms and one double bond, and is made radioactive by the addition of I^{131}-monochloride to one of the double bonds. Admittedly, this iodinated fat is no longer identical with the naturally occurring noniodinated triolein. However, several reports have shown that when this isotopically labeled triglyceride is ingested it behaves similarly to nonradioactive lipids.[1] Thus its use in the study of fat metabolism appears to be sound.

Our group has had a large experience with oral tolerance tests with radioactive fat, and we wish to report at this time our results and their possible significance in three specific areas of study: (1) in patients with coronary artery disease, (2) as a screening device to detect the presence of a defect in lipid metabolism in an asymptomatic individual, and (3) in the evaluation of cholesterol-lowering agents.

Technic

The method we have used is essentially as follows: On the day prior to the test, 10 drops of a saturated solution of potassium iodide is administered three times to block I^{131} uptake by the thyroid gland. Then, after an overnight fast, each patient receives an oral test meal consisting of 25 microcuries of I^{131}-triolein in a total volume of 1 ml. per kg. of body weight of peanut oil. A venous blood sample is taken initially and at frequent intervals thereafter until a peak blood concentration of radioactivity is reached, and then again the following morning at the twenty-fourth hour. The radioactivity in the whole blood and in a trichloroacetic acid precipitated fraction is determined and expressed as a percentage of the initially ingested fat, together with chemical determinations of the serum triglycerides and unesterified fatty acids. Food is withheld until the fifth hour, and the patient remains in bed or in a chair during this interval.

After the tagged fat is ingested, it passes into the small intestine where absorption occurs. The radioactive iodine which circulates in the blood is present in two forms: organic, as part of a lipoprotein molecule, and as inorganic iodide, which is formed by the splitting of the fatty acid linkage during

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†From the Albert Einstein Medical Center, The Sidney Hillman Medical Center, and the Hahnemann Medical College, Philadelphia, Pa.

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its catabolic phase. The organic fraction, which is separated by the addition of trichloroacetic acid normally does not exceed 50% of the total blood radioactivity. Thereafter, the inorganic I^{131} is excreted into the urine where it can be assayed. Normally, less than 5% of the administered radioactivity appears in the stool. In the presence of malabsorption, higher amounts are found.

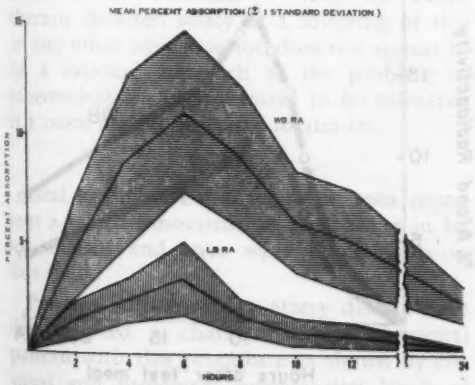
In the study of our blood radioactivity curves, especial attention has been paid to: (1) the time of the peak blood radioactivity concentration, (2) the magnitude of this peak value, (3) the 24 hour activity levels, and (4) the organic fraction to whole blood radioactivity ratio. We appreciate that these values are only a partial reflection of the complete metabolic cycle which is involved. However, they allow for comparative analyses of the results in groups and individuals.

In normal subjects, after ingestion of the triolein test meal, the blood radioactivity rises to a peak usually by the sixth hour, and then gradually declines so that after 24 hours only small amounts remain. The maximum whole blood values range between 10 and 12%, and the lipid-blood values between 3 and 5 per cent. At the twenty-fourth hour the whole blood radioactivity level is between 2 and 3%, and the lipid bound less than 0.5 per cent. The lipid blood to whole blood radioactivity ratio is less than 50% at all times (Fig. 1).

Use of the Test

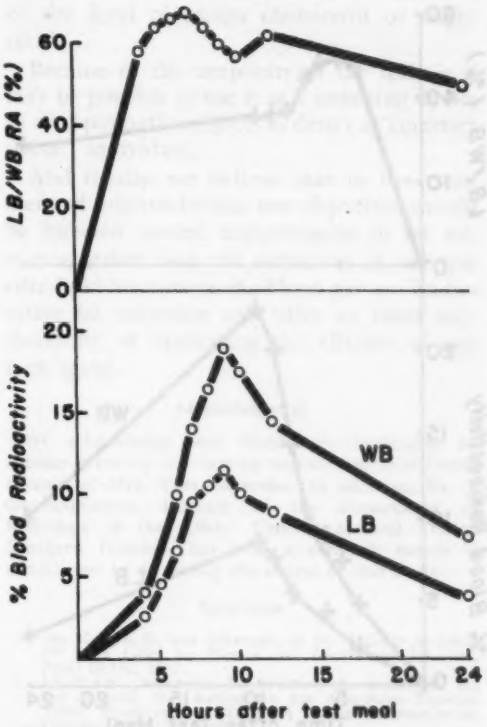
1. Radioactive Fat Tolerance Tests in Coronary Artery Disease. In patients with

FIG. 1



Radioactive fat tolerance tests in normal subjects. (WB = whole blood, LB = lipid blood, RA = radioactivity)

FIG. 2

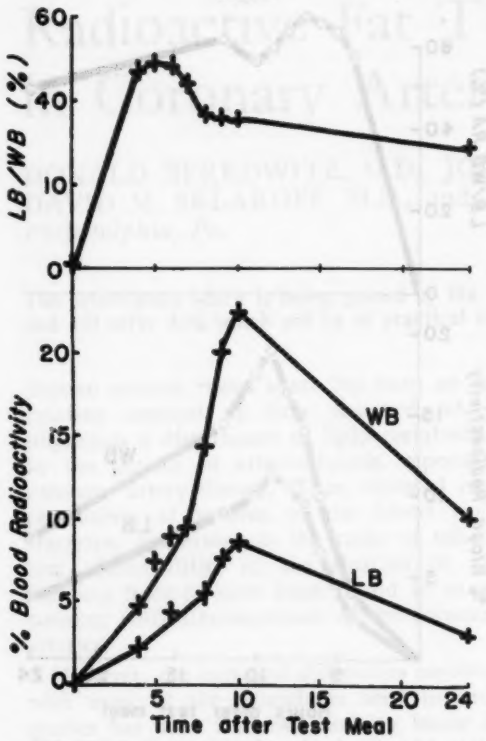


Abnormal radioactive fat tolerance test in patient with coronary artery disease.

coronary artery disease as evidenced by the prior occurrence of a myocardial infarction, radioactive fat tolerance tests have demonstrated marked differences from normal.[2-5] These are characterized by elevated and prolonged postprandial blood levels of radioactivity which persist even after 24 hours. In addition, the ratio of lipid to whole blood radioactivity is increased in many (Figs. 2 and 3). Simultaneous determinations of the levels of triglyceride and unesterified fatty acid show that these also increase postprandially, the increase being greater in the coronary group than in normals. In general, the triglyceride values parallel the blood radioactivity.[6]

Thus, on the basis of our experiences to date, we believe that the radioactive fat tolerance curves obtained in patients with coronary artery disease are indicative of an abnormality in lipid metabolism which may be a reflection of some derangement in the triglyceride fraction. Furthermore, we have

FIG. 3



Abnormal radioactive fat tolerance test in patient with coronary artery disease.

found an abnormal tolerance to radioactive fat much more consistently in these patients than an elevation in any of the serum lipid fractions such as cholesterol, triglycerides, or unesterified fatty acids[7] (Table 1).

It is interesting to note that similar "coronary" patterns have been found in other conditions, notably in diabetes and obesity.[8,9] These observations give further evidence of a linkage between these disease states and may help explain the increased incidence of atherosclerosis which is present in these conditions.

2. The Use of Radioactive Fat Tolerance Tests as a Screening Procedure. If we accept the premise that abnormal fat tolerance is an indication of abnormal lipid metabolism and is apparently characteristically found in coronary artery disease, then the routine use of this procedure as a screening device in asymptomatic individuals may help to identify those who are predisposed to coronary disease before clinical manifestations are present. Our data indicate that approximately 5 to 10% of apparently "normal" subjects in the younger age group (less than 40) and a higher percentage of the older ages show impaired tolerance to radioactive fat (Fig. 4). The prognostic implications of these data can only be assessed by a long term follow-up which we are continuing. The potential of such a test is certainly very readily apparent.

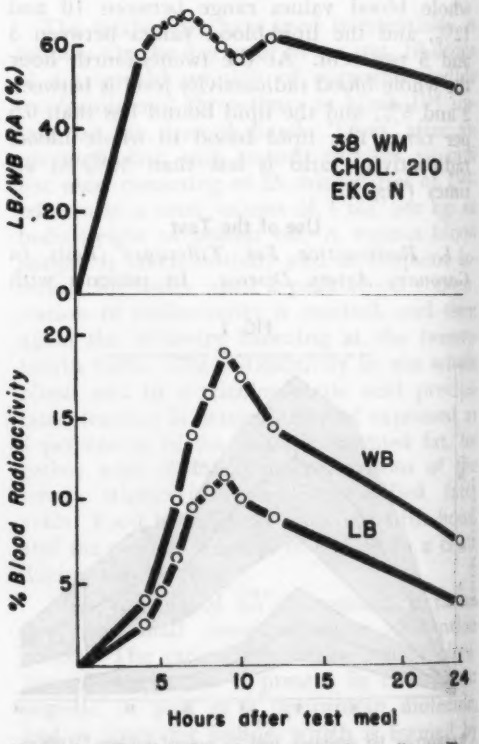
3. The Use of Radioactive Fat Tolerance Tests in the Evaluation of Cholesterol-Lowering Agents. Much emphasis is being placed at the present time on the significance of an elevated level of blood cholesterol as foreboding an early vascular complication. As a

TABLE 1

INCIDENCE OF ABNORMAL TESTS IN CORONARY ARTERY DISEASE
(50 Patients)

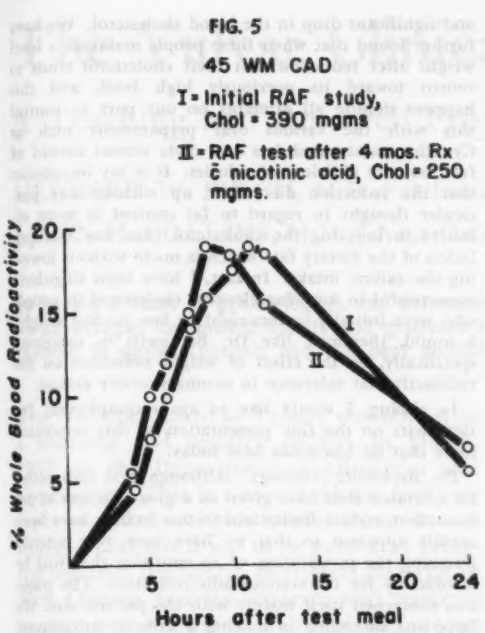
Cholesterol	*Unesterified Fatty Acids*	*Triglycerides*	*RAF Tolerance*
45%	10%	55%	75%

FIG. 4



Abnormal radioactive fat tolerance test in a "normal" subject.

FIG. 5



Radioactive fat tolerance tests before and after treatment with nicotinic acid in patient with hypercholesterolemia and coronary artery disease.

result, the patient who is the victim of such an aberration is usually treated with any one of a number of agents currently being recommended as effective in reducing serum cholesterol, such as nicotinic acid, and certain unsaturated fatty acid mixtures. Our results with these and others made available to us for clinical trial have shown that, although in a certain number of cases a reduction in the blood cholesterol may be achieved, in no case has this been accompanied by improvement in fat tolerance[10,11] (Fig. 5). Thus, therapy directed solely at a lowering of this or any other lipid fraction does not appear to be a rational approach to the problem of atherosclerosis. Improvement in fat tolerance is a more logical objective to aim for.

Summary

Oral radioactive fat tolerance tests represent a recent innovation in our studies in fat metabolism and have wide applications in this field.

Patients with coronary artery disease have demonstrated a characteristically abnormal pattern with this procedure as shown by elevated and prolonged postprandial levels of blood radioactivity. This abnormality is present more consistently than an elevation of the level of serum cholesterol or triglyceride.

Because of the simplicity of the technic it may be possible to use it as a screening device in asymptomatic subjects to detect a "coronary prone" individual.

And finally, we believe that in the treatment of atherosclerosis, our objectives should be directed toward improvement in fat tolerance rather than the reduction of any specific lipid fraction of the blood *per se*. Radioactive fat tolerance tests offer an ideal way, therefore, of evaluating the efficacy of any such agent.

Acknowledgment

We acknowledge with thanks the invaluable assistance given by our isotope technicians, Miss Hettie Brenz and Mrs. Tina Glawaski. In addition, Dr. J. Gershon-Cohen, Director of the Department of Radiology of the Albert Einstein Medical Center, Northern Division, has been a constant source of stimulation to us during the course of this study.

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Discussion (Abstract)

Dr. James A. Kaufmann, Atlanta, Ga. I feel that the subject presented by Dr. Berkowitz is one of the most important and fruitful vineyards in practical medicine and public health today, because it not only deals with our leading killer, but it evaluates a fresh aspect of one approach to the control of this serious disease. If this disease with such a high mortality rate can be controlled, for example, by modification of diet or other practical means, it would be well worth while to attempt to change the dietary habits

of an entire population. However, if definite proof is lacking, then alterations in diet or other regimens may be just an unnecessary burden. It is through methodology such as this that the true answer will be found. Dr. Berkowitz and his group who are working on radioactive fat tolerance studies in coronary artery disease are to be complimented on this and the other fine studies which they have presented.

There are a few specific questions in relation to this paper that I would like to ask. The first is: Since this method of study was originally introduced by Thannhauser and others as a means to study intestinal absorption problems, among other things, I wonder if this group or others are developing methodology for the intravenous administration of radioactive fat so as to eliminate the factor of changes in the intestinal barrier as a factor influencing results, for it would seem that the important thing in coronary atherosclerosis is how the body handles the fat after it has reached the blood stream.

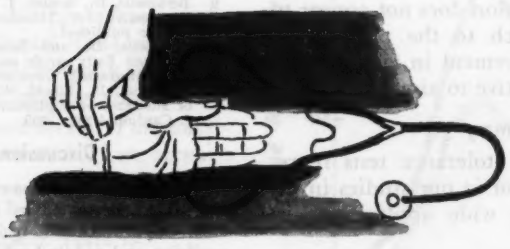
The second question is: You have commented on the lack of change in the radioactive fat tolerance following the treatment of patients with many of the conventional remedies that are now in vogue for the treatment of hypercholesterolemia which are used particularly in the presence of coronary artery disease. I think that the pertinent question is, if these do not change this abnormal fat tolerance, what does? We must answer this to find a practical approach.

The third question which I would like to present for your consideration is that we have had personal experience with over 500 obese patients whose serum cholesterol levels were studied at the beginning of a reduction regimen, and in every case where the initial cholesterol was elevated, follow-up studies were made following the loss of weight and almost invariably, if there has been good weight loss, there was a substantial and significant drop in the blood cholesterol. We have further found that when these people maintain a level weight after reduction that their cholesterol tends to return toward its previously high level, and this happens despite all attempts on our part to control this with the various oral preparations such as Cytellin, unsaturated fats and diets almost devoid of fats, but not deficient of calories. It is my impression that the reduction diet made up without any particular thought in regard to fat content is more effective in lowering the cholesterol than any manipulation of the dietary fats which is made without lowering the caloric intake. In fact, I have been singularly unsuccessful in lowering elevated cholesterol in people who were initially underweight or low normal weight. I would, therefore, like Dr. Berkowitz to comment, specifically, on the effect of weight reduction on the radioactive fat tolerance in coronary artery disease.

In closing, I would like to again compliment Dr. Berkowitz on the fine presentation of this important topic that he has made here today.

Dr. Berkowitz (Closing). Although oral radioactive fat tolerance tests have given us a great amount of information, certain limitations to this technic have been readily apparent so that we have been very actively pursuing the preparation of an emulsion that will be satisfactory for intravenous administration. The problem concerned itself mainly with the particle size. We have just succeeded in making a suitable intravenous tagged fat emulsion, and are studying this now.

We have seen improvement in radioactive fat tolerance in several instances. For example, intravenous heparin will consistently decrease the postprandial blood radioactivity levels, and in some cases, sublingual heparin has also done this. Weight reduction in a previously obese individual has also been associated with improvement in radioactive fat tolerance.



The Vulvar Clinic:

A Teaching and Research Project*

HERBERT W. BIRCH, M.D.,† *Atlanta, Ga.,* and
JASON H. COLLINS, M.D.,‡ *New Orleans, La.*

By having a team of gynecologists and dermatologists, a clinic for vulvar disease has demonstrated its advantages for undergraduate and graduate teaching. Obviously, the patients profit thereby in early diagnosis and the best possible treatment.

THE VULVAR CLINIC at Tulane was started as a teaching and research project in March, 1957, in the Department of Obstetrics and Gynecology. This is a report of the first two years of activity of this special clinic. It was thought that much was to be gained by bringing together the wealth of clinical material in New Orleans and the students and residents in training. Additional value of the project was anticipated from an investigative standpoint in that carefully controlled studies could be carried out with newer modes of therapy. Accordingly, one entire morning of each week was set aside for the Vulvar Clinic.

The Department of Dermatology has also been interested in this project from the start and has provided personnel to be present at each clinic session. This joint effort has been particularly fruitful because of the frequent occurrence of general dermatologic disorders with involvement of the vulva. This also has provided excellent interchange of diagnostic technics, knowledge, and therapeutic armamentarium. The patients benefit from this immediate consultation and are spared the necessity of repeated visits to a number of various clinics before relief of symptoms is afforded.

There are a number of clinical and research laboratories whose services are available in studying the numerous vulvar problems that have been seen. The Obstetric and Gynecologic Research Laboratory provides steroid and other endocrine evaluations. The mycology laboratory and the laboratory for the study of venereal diseases make available evaluation of specific cultures and smears of material from any suspicious lesion. Multiple studies of vulvar biopsies are performed in the Department of Pathology in the University Medical School, and in addition by the dermatologic and gynecologic pathologists. Cytologic smears are frequently obtained and are prepared and screened by the Tulane Cytology Laboratory.

The residents and fellows in Obstetrics and Gynecology at Tulane are all rotated through the clinic as an integral part of their training. This has provided, in concentrated form, an abundance of experience in this phase of gynecology. The students are also encouraged to attend whenever they have "worked up" a patient that is referred to the Vulvar Clinic.

The Clinic has become a center to which many interesting and perplexing problems of the vulva have been referred. Two hundred and twenty new patients have been registered into the Clinic during these first two years. Many of these were referred from out of town and some from outside Louisiana. Most of these patients, however, were referred from other clinics and services at the medical center. The average number of patient visits weekly is 15 but varies from 5 to 25. This has allowed adequate time for considerable discussion of the various phases of interest concerning all the lesions seen. The students, interns, and residents thereby gain maximally from this as an educational experience. There have been 47 different entities of vulvar disease in the new patients admitted to the clinic. These

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Aided by a Grant from the Ex-Residents and Fellows Research Fund.

have encompassed a wide variety of malignant and benign neoplasms, infections, allergies, and malformations.

The Clinic has provided excellent follow-up on 55 of our patients who have had vulvectomy prior to the opening of the Vulvar Clinic. Twenty-eight of these were operated on for benign diseases, while 27 were operated upon for malignant lesions.

It has been our good fortune to obtain follow-up on all of the 128 extensive vulvectomies performed on the Tulane Service over a 13 year period ending January 1, 1959. This is, in part, due to the activities of the Vulvar Clinic. During these first two years of experience there have been 22 new patients admitted to the Clinic whose lesions required vulvectomy. Twelve of these were malignant and 10 were benign. Twelve patients presented with active venereal disease and 63 patients were seen with vulvar lesions and diabetes mellitus. Then in 15 of our new patients, the vulvar lesion was the primary or secondary part of a generalized dermatologic disorder such as psoriasis, pityriasis rosea, neurodermatitis, secondary syphilis, and seborrheic keratosis.

Vulvar Survey

In caring for the numerous and varied problems, an extensive vulvar survey is employed (Table 1). The history is particularly contributory in determining any possible allergy to clothing, drugs, cosmetics or soaps. In the general physical examination similar lesions are searched for on other skin and mucous surfaces. The need for complete pelvic evaluation is obvious and is always done. The wet mount examination is performed in any case where pruritus and leukorrhea are factors. In this way yeast, trichomonas, and hemophilus vaginalis are discovered early in the work-up.

TABLE 1

VULVAR SURVEY

History and general physical examination
Pelvic examination and wet mount
Culture from vagina and vulva
Complete blood count and serologic tests
Darkfield and Frei tests
Studies for Donovan bodies and Ducrey bacilli
Urine and stool analysis
Glucose tolerance test
Photograph
Biopsy

The cultures are for yeast and fungi, as well as for bacteria.

Blood dyscrasias are often found by the blood studies. The patients who have ulcerative lesions are sent to our venereal detection laboratory where smears are made for darkfield examination, for Donovan bodies, and Ducrey's bacillus. By these studies we have discovered the presence of active venereal disease in 12 patients, 4 of whom had syphilis with vulvar lesions and 4 each of granuloma inguinale, and lymphopathia venereum. Biopsy of the vulva is commonly used, particularly in the patients who have a white lesion, ulceration, or tumor. This has been done with a skin biopsy punch under local anesthesia in the Vulvar Clinic. Following the removal of an adequate portion of the lesion a piece of Gelfoam is placed over the site and held with pressure by the patient. This has proven to be effective in controlling the bleeding and we have not seen any difficulties arise from using this method. On the other hand, valuable information needed to properly care for the patient has been obtained without hospitalization. The glucose tolerance test is performed upon all patients presenting with pruritus, regardless of type of lesion, color of lesion, or infective organisms found. A picture is made and it becomes a valuable part of the patient's record. The importance of the biopsy cannot be overstated. It has been utilized in over 90% of our patients and has provided the decisive information in the management of the majority of cases.

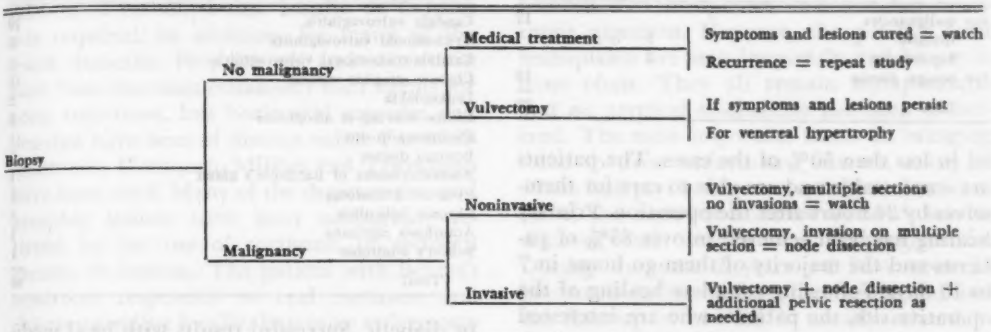
Management of Patients

The management of vulvar lesions after biopsy has been obtained is graphically demonstrated by figure 1. When the biopsy reveals a benign lesion, the treatment is specific local and general medical therapy and the patient is observed. If any recurrence develops, the vulvar survey is repeated and again medical therapy is utilized. Extensive vulvectomy is performed upon patients with severe symptoms of pruritus, burning, itching, discharge and pain that persist over a long period of time despite exhaustive diagnostic survey and prolonged general and specific local medical therapy.

Vulvectomy is also afforded to patients with chronic granulomatous venereal disease whose vulvar tissues fail to return to normal follow-

FIG. 1

MANAGEMENT OF PATIENTS



ing adequate medical therapy and complete irradication of the infective organisms. Chronic hypertrophic residues of granulomatous venereal disease have been found in association with 18% of the 83 cases of vulvar cancer seen on our service over the past 13 years. Whenever the biopsy reveals carcinoma-in-situ, an extensive vulvectomy is performed. Multiple sections of the tissues removed are studied microscopically. If these fail to disclose invasion the therapy is considered adequate. We have had no deaths from tumor in any of the 12 patients with preinvasive carcinoma managed in this way from January 1, 1946, to January, 1959, on the Tulane Service. If invasive malignancy is found by biopsy, the extent of the disease is determined by appropriate cystoscopic and protoscopic examination and a metastatic x-ray series is obtained. The presence of bony or distant metastases are the only contraindications to surgical treatment. The surgical management consists of extensive vulvectomy and bilateral inguinal and extraperitoneal pelvic lymphadenectomy. When adjacent structures are involved, such as the vagina, urethra, bladder or rectum, they are removed.

The procedure of "extensive vulvectomy" that has been used is called "radical vulvectomy" at most centers, but at Tulane we take issue with those who wish to call anything "radical" that relieves pain and prolongs the life of the patient. The procedure includes the wide excision of the entire vulva, including the labia minora and majora, the clitoris, and an additional border of the mons and perineal body. The incision is placed as far laterally as necessary to remove all of the diseased skin plus a sufficient border of normal tissue to prevent recurrence. The medial incision is placed within the vagina at the level of the hymenal ring but is readily moved higher if necessary. The dissection is carried down to the periosteum of the pubis and to the levator ani muscles, thus removing the urogenital compartments as well as the entire vulva. This basic procedure is performed both in malignant and benign disease of the vulva. However, in dealing with malignant lesions, the contents of the ischiorectal fossas are also removed.

This technic was instituted by Dr. Conrad G. Collins, and since January 1, 1946, all patients on the Tulane Service have been managed by a single team. Over this period of time, 128 patients have received extensive vulvectomy for malignant and benign disease (Table 2). The 5 year survival on those operated upon for malignancy is 68 per cent.

The new patients from the Vulvar Clinic requiring vulvectomy are listed in table 3 and are included in the total of 128. Vulvectomy done in this fashion has been shown to be vastly superior to simple, partial or hemivulvectomy. Consequently, these are not done on the Tulane Service. The procedure itself is rapid, safe, and associated with minimal bleeding. Blood transfusions have been need-

TABLE 2

VULVECTOMIES JANUARY 1, 1946, TO JANUARY 1, 1959

For malignancies		76
Invasive	64	
Pre-invasive	12	
For benign disease		52
Total		128

TABLE 3

VULVECTOMIES IN 2 YEARS OF VULVAR CLINIC

For malignancies		12
Invasive	9	
Pre-invasive	3	
For benign disease		10
Total		22

ed in less than 50% of the cases. The patients are comfortable and are able to care for themselves by 24 hours after the operation. Primary healing has been achieved in over 85% of patients and the majority of them go home in 7 to 10 days. Following complete healing of the operative site, the patients who are interested in sexual intercourse are able to engage in it with the same gratification as before. Pregnancy has occurred in 7 of these women, and uncomplicated vaginal delivery of the 12 babies took place.

Diabetic Vulvitis

One of the most common problems encountered in the Vulvar Clinic has been that of diabetic vulvitis (Table 4). There have been 63 new patients admitted to the Clinic with vulvar lesions and diabetes. In 40 of these, the diagnosis of diabetes or prediabetes was made by a glucose tolerance test performed by the Tulane Obstetric and Gynecologic Research Laboratory. Some of these patients had had repeated previous fasting blood sugar determinations and all had had previous tests for glycosuria. Twenty-two patients were frank diabetics and the other 18 were prediabetics (Table 4). Approximately one third of these patients had normal fasting blood sugars and the urines remained negative throughout the tests. For this reason we now immediately use the glucose tolerance test rather than depending upon urine and fasting blood sugar determinations as screening procedures. It has also become apparent to us, in managing the vulvar problems, that the infections are equally resistant whether the woman be prediabetic

TABLE 4

DIABETICS IN VULVAR CLINIC
March 7, 1957, to March 7, 1959

Diagnosis by Ob-Gyn. Research Lab.		40
Frank diabetics	22	
Prediabetics	18	
Known diabetics		23
Total		63

TABLE 5

VULVAR LESIONS IN NEW DIABETICS

Candida vulvovaginitis	10
Trichomonal vulvovaginitis	2
Candida-trichomonal vulvovaginitis	5
Chronic atrophic vulvitis	12
Leukoplakia	2
Lichen sclerosis et atrophicus	2
Carcinoma-in-situ	1
Bowen's disease	1
Adenocarcinoma of Bartholin's gland	1
Pyogenic granuloma	1
Chronic folliculitis	1
Acanthosis nigricans	1
Behcet's syndrome	1
Total	40

or diabetic. Successful results with local medications are only achieved following proper control of the hyperglycemia in both diabetics and prediabetics.

Of these 40 new diabetics, 10 were white and 30 were Negro. The age range was from 19 to 78 with the mean age of 50. The only common symptom presented was that of pruritus. Many complained of additional discharge, sores, burning, tumors, dyspareunia or boils. The duration of symptoms varied from 2 weeks to 20 years with an average duration of two and one-fourth years. The appearance of the lesion was most commonly red, edematous or excoriated, but many were described as being white, atrophic or lichenified. The final diagnoses in these 40 patients are listed in table 5 and, as can be readily seen, infections are directly responsible for the majority of these problems. Superimposed infections were probably present in most of the remainder. In 3 patients there was an associated vulvar malignancy.

The value of knowing that a patient has diabetes when she is taken to surgery for vulvectomy and dissection of lymph nodes is manifest to all, for healing is poor in the uncontrolled diabetic. The therapy utilized in the 40 new patients with diabetes and vulvitis is listed in table 6. In managing the carbohydrate hypometabolism, diet alone was

TABLE 6

THERAPY IN DIABETICS

Diet (1,200-1,800 calories)
Specific diabetic therapy
Specific treatment of Candida
Specific treatment for Trichomonas
Local medications
Surgery (extensive vulvectomy)

sufficient for the prediabetics, and this varied from 1,200 to 1,800 calories with a low proportion of carbohydrates. Insulin or Orinase was required, in addition, for many of the frank diabetics. Proprion gel and mycostatin have been the most commonly used agents for yeast infections, but boric acid capsules and douches have been of distinct value. For trichomoniasis, Floraquin, Milibis and Tricofuron have been used. Many of the degenerative and atrophic lesions have been measurably relieved by the use of cortisone, or estrogen creams, or lotions. The patient with Behcet's syndrome responded to oral cortisone and chlortetracycline locally. Extensive vulvectomy was performed in the 3 instances of malignancy, and in one patient with chronic atrophic vulvitis. There has been no recurrence of any of the lesions managed by surgery in this group.

As can be seen in table 7, the usual period of time before complete relief of symptoms occurred was within 2 to 4 weeks, and the skin and mucous surfaces returned to normal within 3 months. One patient with neurodermatitis and psychiatric problems insists that she has not been benefited despite prolonged medical therapy. One of the patients was referred and we have no follow-up on her. The vulvar skin has not returned to normal appearance in 5 patients followed over 6 months. Two of these have leukoplakia, 2 lichen sclerosis and atrophicus and one has acanthosis nigricans. However, the patients with leukoplakia are seen frequently and biopsy is done often. They all remain asymptomatic and no atypical epithelium has been discovered. The most important factor in bringing relief to these unfortunate women, many of whom had previously received numerous courses of the same medications we used, was to discover and control their hyperglycemia. During the past 2 years we have seen 23 known diabetics with vulvar problems, and the flare-up of vulvitis is usually related to uncontrolled hyperglycemia.

TABLE 7

RESULTS OF THERAPY IN NEW DIABETICS

A. Time to relief of symptoms	
Time	*Number Patients*
1-2 wks.	18
2-4 wks.	16
1-3 mos.	4
3-6 mos.	0
Over 6 mos.	1
B. Time to clinical cure	
Time	*Number Patients*
0-1 mos.	19
1-3 mos.	13
3-6 mos.	2
6-12 mos.	2
Over 12 mos.	3

Conclusions

The Vulvar Clinic at Tulane Medical School has now been functioning for two and a half years. It has already proven to be of great value as a teaching and research project. Improved patient care and increased training benefits for residents are the natural consequences of a concentrated effort by both gynecologic and dermatologic staffs. The Clinic has provided the excellent follow-up so necessary to carry out any valid investigative work. The wealth of experience in the Clinic has shown the value of a thorough survey in managing these difficult vulvar problems. This must include the wet mount, cultures, studies for venereal disease and the biopsy. The glucose tolerance test should be carried out frequently even when the fasting blood sugar is normal and when there is no glycosuria. Prediabetes with transient hyperglycemia has been found to be a definite factor in producing resistance to vulvitis therapy. The Clinic has reduced delay for both the patient and doctor in providing definitive treatment for malignancies of the vulva. Consequently, there is an increasing ratio of early lesions. We anticipate a continued shift in this direction and a resultant rise in the survival of patients treated for vulvar cancer.

Twenty-two Years' Experience in the Performance of 200,000 Prophetic Patch Tests*

LOUIS SCHWARTZ, M.D., *Washington, D. C.*

The author's patch test offers a certain method to determine the presence or absence of sensitizing properties before a product is placed on the market.

THE USE OF THE DIAGNOSTIC PATCH test is attributed to Jadassohn who described it in 1894. However, as early as 1645, Sir Kenelme Digby of London placed a rose petal on the cheek of Lady Hennage and raised a blister to prove that she had "antipathy" against roses. Sir Digby also recognized that certain people had "antipathies" or "sympathies" against certain foods. These facts show that what we now call "allergies" were known several hundred years ago. The word "allergy" was coined by von Pirquet to designate an altered reaction occurring in people who had received intradermal injections of tuberculin and afterwards developed a wheal at the site of a second injection of tuberculin given 7 days later.

The diagnostic patch test has been in use among dermatologists and allergists ever since Jadassohn described it, but the "prophetic" patch test was devised in 1938 by me in consultation with Dr. George Gehrmann, at that time Medical Director of du Pont de Nemours, and Dr. von Oettingen, then Director of the Haskell Laboratories. Du Pont was about to place on the market a new synthetic fiber—Nylon—and asked the Public Health Service what test could be performed to show whether the new plastic would be safe for wearing apparel. We knew that the plastic itself was not primarily a skin irritant but it was desired to learn what percentage of the population, if any, might become sensitized by continuous skin contact with it. The method devised to try to induce sensitization was as follows: Undyed Nylon fabric was placed on the arms of 200 individuals selected at random. The patches were covered and sealed onto the skin with adhesive plaster and allowed to remain for 72 hours. Such contact for this length of time was deemed sufficient to produce sensitization if it were to occur from wearing the Nylon fabric. Simultaneously, a surgical gauze patch was placed on the other arm as a control for comparison between the number of sensitization reactions obtained to Nylon and to the surgical gauze. At the end of the 72 hours the patches were removed and the sites inspected; there were no reactions at any of the sites in any of the 200 subjects.

Ten days were then allowed to elapse for sensitization to develop fully, if it was to develop; then similar patches were reapplied on the same sites of skin and permitted to remain again for 72 hours to learn if sensitization had developed. When the patches were removed at the end of this 72 hours again, there were no reactions under the Nylon nor under the surgical gauze. It was thought this test was sufficient to show that Nylon was not a strong sensitizer, if it was a sensitizer at all. But realizing that a sample of 200 subjects was a small sample compared to the millions who would be wearing the material, it was further decided to make undergarments of the new plastic and have a thousand or more subjects wear them under observation for at least a month to see if any would develop a contact dermatitis at the sites where the Nylon touched the skin. When this trial period of wear was over and no cases of dermatitis developed, it was deemed safe to place the new fabric on the market. The test was named by

*Read before the Section on Allergy, Southern Medical Association, Fifty-Third Annual Meeting, Atlanta, Ga., November 16-19, 1959.

me the *prophetic* patch test because it was meant to prophecy whether the material could be safely marketed.

All of this occurred in 1938, and since then I have performed the prophetic patch test on thousands of subjects with more than a thousand different chemicals and not once have the results obtained been false. The prophetic patch test, or one of its modifications, is now being used by most of our large manufacturers before placing on the market new articles which are to be worn next to the skin. Other dermatologists and toxicologic laboratories[1] are successfully performing the Schwartz prophetic patch test. The prophetic patch test protects the public against dermatitis; it protects the good name of the manufacturer's product; it is necessary in order to obtain casualty insurance; it protects the insurance company and the manufacturer in court in claims of dermatitis having developed from the use of their material; and it also enables the manufacturer to install safety measures for preventing dermatitis from it among the plant employees.

The prophetic patch test when properly devised, performed and interpreted will prevent placing on the market materials which when touching the skin may cause outbreaks of dermatitis. This does not mean that occasional cases will not occur because there is scarcely a substance in the whole world to which some unusually sensitive individual will not be allergic.

The following is a partial list of substances tested by me with the prophetic patch test before they were placed on the market: antimildews such as compounds of phenol, mercury, copper, zinc, chlorophenols, iodophors; insecticides; antiseptics such as G-11, G-4; soaps and shampoos containing these antiseptics; wetting agents, the quaternaries, cationics, anionics and nonionics; hair dyes, hair lacquers, hair wavers, dandruff preparations; plastics and resins; fabric dyes, resin dyes, leather dyes; fabric finishes, finishing oils; glove and shoe leather, shoe linings; paper towels, sanitary pads, and felt.

The Test

There have been modifications of the original prophetic patch test. Some of these advocate the application of patches held on the skin by bandages. Some advocate "open window" patch tests. Some advocate placing the chemical on the skin for 8 hours a day for 5 days in succession and then waiting for 2 days and reapplying it for 5 more days. Some place it on the skin for 24 hours a day for 15 days; but the principal is the same—placing the substance on the skin of a sufficient number of test subjects for a time to see how many of them will be sensitized.

The original prophetic patch test with Nylon was a "closed" patch test. A piece of the fabric one inch square was placed on the skin of the arm of the subject, was covered with a piece of cellophane one and a half inches square, and both were sealed onto the skin with a piece of adhesive plaster 3 inches square. During the years that I have been performing this type of test I have found that the use of a simple Elastoplast coverlet, two by two inches square in the center of which is a one inch square of absorbent fabric, answers the purpose for performing closed patch tests with liquids, greases, semisolids and powders.

All prophetic patch tests are not closed patch tests and the type of test to be performed should be determined by the chemical nature of the material tested and by the ultimate method of use by the consumer.

Before undertaking a series of prophetic patch tests, the investigator will do well to first perform the test on himself to make sure that the material to be tested is not a primary skin irritant. If the material proves to be a primary skin irritant it is not necessary to do tests on more than 2 or 3 subjects to confirm this fact. If the results of the test on the investigator shows that the material is not a primary skin irritant, he can then perform the tests on 10 subjects, and if the results of these tests are favorable, tests can then be performed on 40 more subjects. If these tests are still favorable, 150 more subjects can be tested to make up the full 200 subjects. The prophetic patch test performed in this manner may save the manufacturer money for unnecessarily performing the tests on the full 200 subjects in case it proves to be an irritant on the first 50.

Good judgment must be used in the type of patch test to be performed, the site of the skin to which it is applied, and the method of application. The type of test selected will depend on whether the substance to be tested is a cosmetic, fabric, chemical, a volatile substance, a

liquid, or a solid. Control patches must be applied with similar products already safely marketed. These precautions are necessary to arrive at a valid conclusion as to the irritant properties of the substance under actual conditions of use by the ultimate consumer.

In the prophetic patch testing of fabrics to be used as wearing apparel, a piece of the fabric one inch square is placed in the center of an Elastoplast patch and applied to the skin of the arm, the thigh, or the back of the test subject. It is allowed to remain in place for 72 hours. At the end of this period it is removed and the sites of the patch inspected. It is best to wait 5 to 10 minutes after the removal of the patch to see if erythema develops or, if present, soon disappears. Only a persistent erythema is counted as a positive test. The second series of patches, called the "challenging" patches, are placed in a similar manner on the same areas of skin, 7 to 10 days after the first series is removed, this to provide for any localized allergic reactions. Before the second series of patches is placed on the skin the subjects are instructed to report the appearance of any reactions which may occur at the sites of the patches during the interim. It is not uncommon for such reactions, called late reactions, to appear.

The challenging patches are also allowed to remain on the skin for 72 hours, at the end of which time they are removed and reactions noted as described above. The subject is instructed to report the occurrence of late reactions should any develop. Only after 3 days have elapsed from the time the final patches are removed, are the final results noted. It is in this 3 day period that late reactions usually occur. It is not uncommon to note that the site of the first application which showed no reaction becomes inflamed at the same time that the late reaction on the challenging site appears.

Here I will not go into the manner of grading reactions into degrees of 1+, 2+, 3+ and 4+, but all true allergic reactions of whatever grade are eczematous in character and persist for several days or even weeks. I will say a few words regarding doubtful reactions. Sometimes when a patch is removed there is a mild erythema at the site of the patch, not sufficient to be termed a 1+ but still more pink than the skin around it. It is my custom to re-examine such patch sites 24 hours later. If they still persist, I grade them positive; if they have disappeared, I call them negative.

All cosmetics are not tested in a similar manner.[2-6] Skin creams, powders, appropriate dilutions of soaps and other nonvolatile preparations, can be tested by the closed, covered patch test method, especially if a control patch of a similar substance which has long been on the market is used on the other side of the body as a control.

Hair dyes[3] containing oxidizing dyes and alkalies, hair wavers containing alkalies, and hair tonics containing irritants, are not to be sealed onto the skin under a covered patch because such substances when sealed onto the skin act as primary skin irritants and will cause reactions on most skins, whereas in ordinary use they are not covered and sealed onto the skin and are often washed off soon after application. With such substances "open prophetic" patch tests are performed by painting the material on sensitive portions of the skin such as in the antecubital space, behind the ears, or the popliteal space. The area of skin to be painted should be at least one square inch. The substance is allowed to dry on the skin before the subject is permitted to leave. At the end of 24 hours the subject returns; reactions, if any, are noted, and if there are no reactions the same area of skin is repainted with the substance on 2 more days. If there is a reaction at any time, it ends the test for that subject. If there are no reactions after 3 applications, the subject is asked to return 7 to 10 days later (the period allowed for allergy to develop) and the same procedure is again repeated for 3 successive days. The application of a control patch with a similar product sold safely for a number of years should be performed in the same manner on the corresponding portion of the skin on the opposite side of the body.

In testing nail-lacquers and lipsticks containing photosensitizing dyes, open patch tests should be used to give light a chance to act on the photosensitized skin. Nail-lacquer bases intended to remain on the nails for several days should actually be tested on the nails as well as on the skin.

In performing prophetic patch tests with articles meant for wearing apparel,[2,7,8] such as fabrics or leather, closed covered patch tests

can be used, always remembering to use a control patch on the other side of the body.

Discussion

There are possible shortcomings to the prophetic patch test. For instance, the systemic effect which may result from the absorption through the skin of small amounts of the test substance; the evaporation of a possible volatile irritant from the patch; the small amount of the substance on the patch as compared with the larger amount that actually touches the skin of the ultimate user; the short time of exposure in the patch test as compared with the long period of actual usage. All these objections are valid but are overcome by the fact that the prophetic patch test, when found to be safe on 200 subjects, should be followed by an actual usage test in a small community or on at least a thousand control subjects who are under observation for at least one month.

To overcome some of the objections enumerated, modifications of the patch test have been proposed. The principal one of these is the repeated insult test of Draize.[9] In this method the material is applied to the skin of the test subject for 24 hours, removed, and followed by a 24 hour rest period. The test substance is then applied to a different skin site for the same length of time and then removed followed by a 24 hour rest period. This is repeated for 10 consecutive exposures, exclusive of Sundays and nonwork days. Following the 10 individual exposures the subject is given 10 to 14 days rest, after which one challenging application is made to one of the 10 original application sites. A comparison of the reaction following the retest, with the average reading of the 10 original applications permits an appraisal of the sensitizing propensities of the test substance.

A comparison of the results obtained with the Schwartz method and with the modified Draize method proposed by Shelanski was made by a toxicological laboratory and the Schwartz method showed a larger percentage of reactions than did the modified Draize method.*

In my actual experience, when the prophetic patch test on 200 subjects showed no more reactors from a test material than from the control material, there was no trouble after the material was marketed even though a trial usage in a small community or on a thousand control subjects was not done.

In the few instances where the prophetic patch test from the test substance showed more reactions than from the control substance, and against my recommendations, the manufacturers placed the test substance on the market, cases of dermatitis soon were reported.

On the other hand, some products tested by others by unsuitable patch test methods (such as closed patch tests when open patch tests should have been done, or vice versa, or where control patches were not used) were pronounced to be unsafe for use. When these were tested by me in a proper manner, using proper controls, they were found to be safe for use, placed on the market and are still sold without causing any undue trouble.

The reactions produced by the prophetic patch test must be carefully read and compared with the reactions produced by patches with a control substance before a judgment is made as to the safe use of the product. No test is better than the person who performs it.

Some dermatologists have recorded severe reactions from diagnostic patch tests. Even systemic reactions such as malaise and elevation of temperature have been reported. There have also been cases reported of the spreading of reactions to large areas of adjacent skin; reactions at distant portions of the body have also been reported.

In my experience with the prophetic patch test performed in the manner I have described, I have obtained no reactions of a greater degree than 2+ on other than the first 10 persons. On the first 10 I have obtained some severe reactions, but those substances which gave the reactions were not placed on the remaining 190 subjects. The reactions have always been confined to the actual site of the patch test. I have seen no systemic reactions. On myself, on whom I first try unknown substances, I have had reactions as high as 4+, that is, blisters and superficial ulceration, but never any spread to other portions of the skin nor any systemic reaction. In my last series of tests of 92 synthetic detergents in which I placed more than 10,000 patches on the skin of more than 1,000 subjects, I found only three reactions of greater severity than

*Unpublished report of Industrial Toxicology Laboratories, Philadelphia 4, Pa.

1+, after I screened them on the first 10 subjects.

Medicolegal Aspects

Before undertaking to perform prophetic patch tests the subjects to be chosen should be informed of the nature of the chemicals and the purpose of the test. They should be told it is possible that some of them may develop reactions at the site of the patch. They should also be told that tests had already been performed on the experimenter and that the chemicals were found not to be primary skin irritants nor sensitizers to him, but that this does not mean that some of them may not be irritated by the substance and that they are being paid for this chance which they are taking.

After the tests have been performed and the substance has been found to cause no reactions on the 200 test subjects, or to cause no more reactions on them than from a substance which has been on the market for years without causing trouble, it is still possible that there may be some individual users who may be allergic to the substance and develop dermatitis from using it. If such persons institute suits against the manufacturers it will prove a strong factor for the defense if the manufacturer proves that prophetic patch tests had been performed by reputable physicians and that the substance passed the prophetic patch test. Therefore, if the plaintiff's dermatitis is actually due to allergy to the substance, the plaintiff is an unusually allergic or idiosyncratic person and the dermatitis is not due so much to the sensitizing property of the substance as to the unusual, unfortunate, abnormal condition of the plaintiff's skin.

Conclusion

The prophetic patch test devised 22 years ago and used by many manufacturers and dermatologists to test substances to be placed on the market has proven itself to be able to fulfill its intended purpose.

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Discussion (Abstract)

Dr. Marion T. Davidson, Birmingham, Ala. To begin with I want to congratulate Dr. Schwartz on this monumental and voluminous piece of work. Making 200,000 patch tests, even spread over 22 years, is quite a feat. I know of no place outside of a large industrial plant or a large government department, where so many people could be enlisted in such an endeavor. This study is a guide to all other such endeavors. It has been extremely valuable to the makers of synthetic materials of whatever derivation, and of use in avoiding the enormous losses involved should they proceed to use a large amount of materials later found to be unusable due to deleterious effects. It has also been most valuable to the general public in avoiding losses involved in the purchase of materials found later to be harmful.

My own introduction to sensitization to synthetics came shortly before World War II in the person of an asthmatic man. I had been unable to help his asthma by my then routines of testing, elimination and desensitizations. He came in one day and told me that he had noticed that he had asthma whenever he wore a certain necktie. On inspection it was found to be made of Rayon and I obtained a small amount of undyed Rayon and one of Nylon and put them on patch tests. Within a few hours a red, itchy area appeared under the Rayon test while the Nylon test remained clear. I did not go through any of Dr. Schwartz's routine, but merely advised the patient to go home and eliminate from his and his wife's wardrobes all clothing and other materials made of or containing Rayon. He was immediately better and when seen some time later reported that he had had no further asthma since getting rid of the Rayon.

The patch test is simple to apply and I need not discuss it except to mention some of its pitfalls which may be illustrated by the case of a woman patient who had a rim of eczema at the hair margins pointing definitely to something being applied to her scalp. I had her bring in her hair lotions and had a simple problem as she used only one. This bottle contained no statement of ingredients and so I moistened a pledget of cotton and put it on her arm and waited a while. As she experienced no discomfort I let the pledget dry and then covered it with a patch test. I told her to remove the patch at once should any discomfort occur. She did not come back for several days and when she did come she said the patch had been very uncomfortable but she had left it on for me to see. On removing the patch she had a hole through the full thickness of her skin and just the size of the pledget of cotton. I wrote the manufacturer for the formula which he sent me at once. One ingredient was cantharides which has been used as blistering material ever since the days when many painful complaints were treated by blistering. The cantharides was a skin irritant and allergy had nothing to do with producing the eczema.

Dr. Schwartz mentions the question of legal responsibility involved in attempts to stimulate sensitivities in otherwise healthy people. Such an attempt if successful, might involve a physician in private practice in embarrassing legal complications. In Dr. Schwartz's work I presume that the industrialists or the government department assume all risks.

My experience with the patch test has been mostly on the negative side in showing that the materials being tested were not sensitizers. I presume Dr. Schwartz's work is responsible for this in having shown manufacturers which materials could be used with little chance of sensitivity developing. My only reaction recently has been a "dud." I put Nylon and Rayon on patches and soon the patient pointed to one and said that one was itching up a storm. I removed it at once and found an area of redness under the patch but this faded quickly, and I reapplied another piece on a different site which proved to be entirely negative. I concluded that the patient had had some irritant on her skin unnoticed at the first site.

In conclusion, let me say that I consider the prophetic patch test a most important addition to the allergic armamentarium of tests. We have almost all, benefited by it unawares, and we owe Dr. Schwartz a debt of gratitude for his unselfish and untiring efforts.

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Placenta and Cord — Vulnerable Fetal Support*

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The author considers causes of fetal death which may be blamed to disturbances of the placenta and/or cord which lead to anoxia of the fetus.

THE OBSTETRICIAN, of all people, is well able to appreciate how very early in life the risks to survival begin. Today we are often reminded that atomic weapons could destroy the works of man and perhaps all human life as well. This awesome possibility should be hardly more disturbing, however, than realization that for three fourths of a year as a fetus, each human life has virtually been hanging by a thread. Circulation through the cord is easily compromised and the placenta, if originally adequate, is so vulnerable to accident, dysfunction or premature aging as to justify wonder at the near miracle of each live birth.

For perhaps too many years, obstetricians have pointed with pride to a remarkable reduction in the maternal mortality associated with labor and delivery. For more than a generation, while so satisfied with the reduction in maternal mortality, we have accomplished relatively little to increase the chances of fetal survival. Perhaps we have been inclined to take it for granted that mere periodic review of the causes of fetal death would in some way result in a reduction in the numbers of fetal deaths occurring during labor and delivery. At least we have recognized the need for reductions in both maternal and fetal loss, though to date our efforts have not seemed so effective in reducing perinatal mortality.

For years, in the efforts we have made to reduce neonatal deaths, we have sought to prevent premature births and been largely occupied with the care of premature infants. Perhaps it is unfortunate that, by common usage, we have considered fetal loss in terms of gross or "uncorrected" and true or "corrected" figures. The acceptance of certain causes of fetal death as "correctable" is likely to perpetuate a feeling on the part of all of us that a certain inevitable fetal loss is to be expected. Macerated stillborns for instance have so long been considered "correctable" in reports of fetal mortality that both antepartum and intrapartum deaths have received relatively little attention. At least we have not seemed to be disturbed by the persistence and frequency of "ill-defined or unknown cause" as an explanation for many fetal deaths in virtually all reviews of fetal mortality. Only 5 years ago, in a review of fetal mortality in the city of New York for the years 1946-1953, for instance, Gold[1] concluded that 41.6% of all the stillbirths reviewed could, in the light of available information, only be ascribed to "ill-defined or unknown cause." Certainly no reports of maternal mortality would have been acceptable in the last decade which failed to ascribe a more specific cause for the deaths of nearly half of the cases reviewed. Today, however, we are more likely to ascribe fetal deaths to one of the causes of anoxia and greater interest is evident in the possibly preventable causes of stillbirth.

Anoxia Due to Placental Causes

About the time of Gold's report, data indicating fetal oxygen deficiency during uterine contractions in even normal labor, as well as the risk of more serious degrees of anoxia when the placenta was inadequate or possibly postmature, heightened the suspicion that a goodly proportion of the deaths ascribed to ill-defined or unknown cause might, upon more careful analysis, be due to antepartum or intrapartum asphyxia of the fetus. The very existence of the so-called postmature syndrome continues to be ques-

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tioned by many obstetricians. Recent literature seems to indicate a more general acceptance of the concept that there is real risk of a placental dysfunction syndrome, however, and that this risk is considerable when the baby is dependent upon an abnormally small or a postmature overdue placenta for oxygen and nutrition.

In 1956, Frost[2] reviewed the hospital records of the 213 stillbirths which had occurred in the Buffalo General Hospital during the years 1946-1955 inclusive. During that 10 year period 61 fetal deaths (28.6% of the stillborns) had in effect been ascribed to the ill-defined or unknown category. Frost's careful study of the labor records indicated that 62% of such poorly ascribed deaths occurred before the onset of labor, whereas 21% of the stillbirths occurred during the first stage and the remaining 17% during the second stage of labor. He noted significant differences in the sizes of the babies and in the circumstances with which the intrapartum deaths were associated.

Among the 12 cases in which fetal death occurred during the first stage of labor, the average weight of the baby was 4 pounds 1 ounce, the average duration of gestation 35.4 weeks. Prolonged labor seemed an associated factor in 50% of this group, whereas prematurity and suspected placental deficiency were both associated with 25% of the fetal deaths occurring during the first stage of labor.

Ten babies died during the second stage of labor. The average fetal weight in this group was 5 pounds 15 ounces, the average duration of gestation 39.3 weeks. Frost concluded that deficiency of the placenta or compression of the cord was demonstrable in 70% of this group. Hard labor (defined as contractions lasting 45 seconds or longer, less than 3 minutes apart, for from 3 to 7 hours) was associated with the death of 50% of the cases in which the fetus died during the second stage of labor. It is interesting that no case of fetal death occurring during the second stage of labor was associated with prolonged labor, though precipitous labor was noted in 2 of the 10 cases and noticeably "hard labor" was frequently recorded.

Considering the data reviewed from the records of the Buffalo General Hospital, it seems evident that if an investigator re-evaluates ascribed causes of fetal death with a suspicion that many of those originally regarded as due to "ill-defined or unknown" cause were associated with fetal anoxia, it is not difficult to blame unusually hard and frequent uterine contractions or a grossly inadequate small placenta for an evident failure to maintain fetal oxygenation during labor and delivery. Is there anything to be gained by shifting the blame for a stillbirth from some ill-defined or unknown cause to the fetal anoxia associated with precipitous delivery or the deficiency likely with an unusually small or extensively damaged placenta? If there is anything to be gained, it might become apparent in an increased awareness of the danger inherent in really hard and frequent uterine contractions. In addition to the risk that such uterine behavior will seriously interfere with the transfer of oxygen from maternal to fetal circulation, Hon,[3] Prystowsky[4] and Hellman[5] have recognized a second danger inherent in prolonged and unusually hard uterine contractions. So long as the cervix offers considerable resistance in a vertex presentation, myometrial forces create an appreciably increased pressure within the compressible fetal cranium. If appreciable this increased pressure results in a noticeable slowing of the fetal heart rate, and a correspondingly poorer circulation of the already poorly oxygenated fetal blood.

Have obstetricians been reluctant to ascribe fetal loss to placental failure simply because we cannot readily demonstrate such placental deficiency? Consider that failure of placental development after nidation accounts for a large proportion of the infertility so frustrating to patient and doctor alike; that inadequacies of the early placenta account for a large proportion of the fetal loss due to spontaneous abortion; and that prematurity, the chief cause of death among live born infants, is almost always due to failure of the placenta to inhibit the onset and forces of labor until such time as the child has a better chance to survive. Consider also that abnormal implantation of the placenta, the varying degrees of praevia and the blood loss due to marginal sinus or vasa praevia, are all recognized causes of occasional fetal loss. Still other pregnancies seemingly progress normally in spite of what eventually proves to have been a clinically imperceptible de-

gree of placental deficiency, only to terminate in sudden abruption of the placenta at the onset of labor, and another stillbirth. More recently emphasized is the risk that fetal anoxia, developing during labor is more likely to be observed with precipitous hard labor, and most likely to become evident if the placenta has become "senile," (in other words when the patient is "overdue"). When placental dysfunction is suspected during early labor, the placental deficiency may have existed before the onset of labor or it may have developed because of imperceptible changes likely but not inevitable when gestation is prolonged.

All of these possible entities add up to the realization that directly or indirectly, the placenta might well be recognized as that unpredictable and uncontrollable quantity which, at any time, with or without warning, may defeat the obstetrician's best efforts. When fetal loss has occurred in the past, we have certainly been too willing to blame a variety of coincidental or perhaps precipitating incidents, as: a fall or a fright for the occurrence of abortion; a mild or terminal toxemia for sudden abruption of the placenta; too much activity for the occurrence of premature labor; and too much sedation or anesthesia for intrapartum asphyxia and the loss of an apparently normal child at term. If we are critical and careful in our appraisal of these situations, however, we will often find evidence that at a critical time the placenta proved inadequate, that it was unable to maintain nutrition of the early embryo, inadequate to prevent the development of the contractions which resulted in premature labor or abruption, or simply unable to keep the fetus oxygenated during the course of a prolonged or, even more likely, during the progress of a rapid precipitous labor. The latter seems not infrequently associated with the otherwise unexplained death of a normally developed fetus at term.

Obvious and acute placental deficiency develops when placenta praevia or premature separation deprives the fetus of oxygen with perhaps fatal abruptness. With the low lying placenta, even when an asphyxiating area of placenta does not separate prematurely, the site of cord attachment may be compressed between the sacral promontory and the engaging fetus. Stallworthy[6] has reminded us that the risks inherent in the posteriorly implanted low lying placenta make it a particularly dangerous complication of labor. A less frequently recognized cause of placental dysfunction may develop when the membranes rupture early and a considerable quantity of the fluid escapes from the uterus. It seems reasonable to expect that considerable contraction of the uterine wall will result as a response to the rapidly decreased volume of amnionic fluid. Such contraction is likely to result in some disruption of the placental site and interference with circulation in the intervillous spaces. This risk occasionally proves one of the very real dangers of early rupture of the membranes, and is most likely when there is no presenting part filling the lower segment to limit the escape of fluid.

Anoxia Due to Disturbances of the Cord

Today there seems much evidence that if we are to reduce the fetal loss associated with labor and delivery, we might well give considerable more thought to the cord and placenta, upon which fetal survival so obviously depends. Accidents of late pregnancy or labor which interfere with circulation through the cord are a recognized not infrequent cause of fetal distress and stillbirth. Tancer and Reuss[7] have recently reported the occurrence of this complication in one of each 380 deliveries. Instances of occult prolapse of the cord were not included in their review.

It is important to remember that evidence of fetal distress led to the discovery of less than 20% of instances of prolapse of the cord in their cases and for this reason they recommend vaginal examination promptly whenever the membranes rupture. Such precautionary vaginal exploration would seem particularly indicated when the vertex is not presenting. They observed that prolapse of the cord was discovered in one case per each 730 vertex presentations, once per each 38 breech presentations and once per each 15 cases of transverse lie with a shoulder presenting. Among the 76 cases Tancer and Reuss reviewed, the over-all corrected fetal mortality was 42.3 per cent. Fetal loss seemed less affected by the presentation or by the method of delivery, and seemed largely determined by the promptness with which delivery was accomplished after prolapse of the

cord was discovered. Prompt vaginal delivery when conditions seemed to permit, or prompt section when vaginal delivery did not appear safe, resulted in a fetal loss of only 10.9 per cent.

When an expectant plan of management was elected, however, all babies were lost regardless of the presentation. When section seems advisable some delay usually appears inevitable. Tancer and Reuss suggest, therefore, that spinal anesthesia should be given immediately to halt labor while preparations for delivery by section are made as rapidly as possible.

This precaution they believe will save babies otherwise likely to be lost within the time necessary to set up and deliver by section. Walker[8] noted that fetal distress was due to strangulation or entanglement of the cord in only 2.5% of the multipara and in 1% of the nullipara in his series. It is evident that many vaginal examinations will be necessary to find the occassional instance in which an otherwise unrecognized prolapse of the cord would be certain to result in a fetal death.

Maturity of the Fetus

Several other obstetric entities are, however, more generally recognized as likely to increase the risks to the fetus near term or during labor. The dangers of being prematurely born for instance are too well known to again warrant discussion. A less generally accepted risk to the fetus may become apparent, however, if pregnancy is prolonged beyond the usual period of gestation. In 1902, Ballantyne[9] was perhaps the first to note an interesting difference between premature and postmature babies. He believed that "premature babies can with difficulty be kept alive after birth, whereas the postmature child is not likely to be born alive."

Nesbitt[10] in reviewing the term deliveries at the Johns Hopkins Hospital during the 5 years 1950-1954, found a 6 times greater incidence of intrapartum death when pregnancy has seemed prolonged. Ballantyne and Browne[11] had both expressed the belief long ago that postmaturity carries an increased risk chiefly because of a greater chance of disproportion due to the excessive size of the postmature baby, and for which reason they had advocated induction of labor at term in order to avoid the dangers of overly large babies.

Calkins[12] has long believed, however, that fetal growth does not continue after the fetus reaches term, and has emphasized that as the placenta ages its efficiency decreases to a point where the baby may actually begin to lose weight if pregnancy is appreciably prolonged beyond the expected date of confinement. Calkins has long emphasized that the size of the baby is more dependent upon placental size and adequacy than upon the duration of the pregnancy. This suggests that if an infant proves oversized at full term it will have acquired most of its excessive size by about the 260th day of gestation. For this reason Calkins believes that the disadvantages of inducing labor in spite of an unripe, unprepared cervix should not be undertaken as a means of avoiding a larger baby because the child would not be getting larger though the mother is allowed to "go over her due date." Kamperman[13] has also expressed belief that after the due date the baby may actually begin to lose weight, and that at least statistically, the longer after the 20th day of postmaturity the smaller will be the baby.

Thus for a number of years the risks of postmaturity were considered chiefly in terms of fetal size. There was little consideration of the ability of the postmature placenta to keep the child oxygenated, really little consideration of what was happening during uterine contractions. All of us realize that the fetus depends for its growth and development upon an adequate supply of nutrients, particularly oxygen which must be received by way of the placenta. It seems impossible that we have been so slow to realize the importance of maintaining oxygenation of the fetus. Walker[8] has repeatedly emphasized that decreasing oxygen supply, due to changes in the placenta as pregnancy becomes prolonged, is the chief factor in many so-called "postmature" deaths of the fetus. His published data indicates that actual measurements of the oxygen available to the fetus lend definite support to those who, on purely clinical grounds, have continued to believe that postmaturity may be dangerous for the child.

Clifford[14] has reported that prematurity with an incidence of 9% accounted for 36% of their fetal deaths, whereas postmaturity

with an incidence of 6% accounted for 30% of their perinatal loss. Clifford has repeatedly described the now widely recognized entity of a baby born some weeks after the expected date of confinement, and which appears to be of less than average weight at term but usually proves to be of average length, with a loose skin suggesting dehydration and with skin, cord, and amniotic fluid deeply stained yellow to brown. Such a child is often born dead, and if born alive often soon dies of respiratory distress. Many now believe that the unusual features of the infants Clifford described must be the result of placental dysfunction and might well be anticipated when pregnancy is prolonged. This point of view seems supported by the studies demonstrating that the human placenta becomes less and less efficient after maximum function at about the 36th week of gestation.

Calkins has recently emphasized that the dangers of postmaturity should certainly be considered when the baby (and therefore most certainly the placenta) appears to be surprisingly small and has emphasized the fact that he has noted no fetal deaths from placental causes when the baby was large. It appears therefore that we should be most apprehensive concerning the patient who seems to be "behind schedule" in her last trimester. Is she really about due, with an undernourished fetus starved by an inadequate placenta, or is she really behind schedule with a still premature baby? A smaller than expected baby as term approaches may certainly indicate inadequacy of the placenta. Such a pregnancy may reach term with an already poorly nourished child deprived of oxygen to a dangerous degree should uterine contractions become prolonged and "hard." There is no situation in obstetrics where alert attendants and a thoughtful obstetrician are more essential. Many have questioned the advisability of inducing labor when the cervix is not ripe. We have all questioned a section *when the child is still immature.* We might well recognize also the risks of permitting a possibly poorly nourished, probably poorly oxygenated, evidently smaller than expected baby to experience the anoxia of the rather rapid labor that can usually be anticipated after pitocin induction when the placenta is inadequate or postmature.

Today's concept of placental dysfunction as a cause of so-called "ill-defined fetal death," might well include what the older clinicians referred to as "habitual death of the fetus." Occasionally, with no evidence of disproportion and an apparently normal baby at term, heart sounds would disappear during the latter part of the first stage or during the second stage of a rather short labor, and delivery revealed a perfectly normal but stillborn infant. Older clinicians were impressed by the possibility that such an unexplained intrapartum fetal death was likely to recur in the same individual in subsequent pregnancies.

In an example of another type of case now likely to be regarded as due to an "inadequate placenta," pregnancy would seem to be progressing normally. Late in the 8th or early in the 9th month of gestation, though her last prenatal examination had suggested a still small baby, the patient would report the rather abrupt onset of frequent pains. On admission to the hospital, the heart sounds could not be heard. Rapid progress was apparent and as the membranes ruptured only a small amount of highly stained amniotic fluid was noted. At delivery, the stillborn fetus appeared surprisingly small, with a noticeably small atrophic looking placenta. In connection with such a story, with no signs of renal disease nor of syphilis, Kellogg[15] spoke of "premature aging of the placenta" typified by a rapid labor, highly colored fluid, a surprisingly small stillborn baby and an avascular looking placenta less than half the weight of an average sized placenta at term.

Does such a sequence of events really represent premature aging of a formerly normal and adequate placenta, or was the placenta always smaller than the usual ratio of 1 to 6 would indicate that it should have been? The possibility of such inadequacy from the earliest stages of placental development was emphasized in 1950 by the work of Smith and Smith.[16] Hughes[17] has long believed that endometrial deficiencies may account for inadequate nutrition in the very earliest critical stages of placental development with resulting inadequacy of the placenta, and secondarily abnormalities in fetal development. For cases of habitual abortion Hughes has favored treatment before conception, to

assure an optimal endometrium, whereas the Smiths have emphasized the postconceptional addition of increasing amounts of stilbestrol to assure greater vascularity of and functional adequacy of the placenta.

It now seems probable and more likely if pregnancy has seemed prolonged that even an originally normal placenta may become functionally deficient. A short precipitous delivery if characterized by long periods of uterine contraction, materially reduces blood flow into the placenta and the exchange of oxygen, mother to fetus. Such relatively long periods of fetal anoxia may be extremely dangerous for the fetus, particularly if labor begins when a fully developed baby is depending upon a past its peak, poorly functioning, postmature placenta for oxygen.

Effects of Anoxia

It is certainly important to realize also, that the causes of central nervous system injury among infants who survive birth, only to develop as mentally retarded, spastic children and the causes of many intrapartum fetal deaths are now recognized as one and the same etiology. Certainly it is time we agree that fetal injury or death is more likely to be caused by asphyxia than by trauma. In most instances placental dysfunction accounts for fetal anoxia and the severity and duration of the anoxia determines the extent and severity of the damage sustained by the fetus. If this be true, no phase of the management of labor is more important than early recognition of fetal distress. As a rule, we must depend upon changes in the rate of the fetal heart sounds to indicate impending or obvious fetal distress. Therefore we should watch for signs of fetal distress especially when the dangers of placental inadequacy might be anticipated. When we do suspect placental dysfunction we might first look for any maternal factor likely to increase the mother's consumption of oxygen, from which supply the needs of her fetus must also be met. Such factors as maternal fever, acidosis, hypertension, cardiac or pulmonary dysfunction all reduce the oxygen available to the fetus. Second, we should watch for anything that will reduce blood flow across the placenta, as a lowered maternal blood pressure or the increased resistance to the passage of blood that results whenever there is a tightly contracting uterus. As surely as maternal hypotension and shock, a tightly contracted uterus deprives the fetus of oxygen. Relaxation of the uterus between contractions therefore *is* essential, not only to conserve the mother's strength and peace of mind, but to make certain for the sake of her baby that adequate quantities of oxygenated blood pour into the placenta between pains.

Prophylactic Treatment

Before the onset of labor, whenever placental deficiency seems a possibility, Walker[8] believes we should induce labor not later than the 40th week. One word of caution, however, it seems likely that induction may not be safe simply because labor *can* be easily induced. The patient whose placental function is not impaired may be more difficult to induce, but she is less likely to go into the precipitous type of labor that can be so damaging to her child. It is ironic but must be true that the patient whose uterus is most responsive to oxytocin might well be the one whose poorly functioning placenta is not producing enough hormone to avoid prolonged uterine contraction. This is likely to be the very same uterus that will not provide sufficient oxygen to the baby once good hard uterine contractions are initiated. Let us at least give thought to the possibility that for the sake of the child the patient in whom labor is most easily induced should in fact be delivered by cesarean section. This is likely to be true only if the fetal heart sounds suggest fetal distress during the contractions of early labor. On the other hand patients showing resistance to induction by oxytocin could be regarded as much safer patients to induce! A trial of very dilute oxytocin solution has been recommended as just such a therapeutic test and may prove to be a valuable aid, if the fetal heart rate is carefully evaluated during and following contractions of the uterus as the Pitocin-induced pains begin.

Greenhill[18] has estimated that if we attempted to avoid the development of fetal anoxia during labor by agreement that in all cases suspected of fetal distress the mother is to be given oxygen by mask, this practice would probably result in the administration of oxygen during labor to approximately 15% of our patients. To now suggest the indications for such prophylactic use of oxygen would obviously be but another listing of the

clinical observations that might suggest the possibility of deficient placental function.

There seems no way to minimize the risks of fetal anoxia other than to keep in mind the possibility of placental deficiency all of the time. Is there reason to feel that such vigilance as this would require is our obligation? Does human reproduction really require such careful observation of mothers and of fetal heart rates during labor? Certainly there is evidence that some babies die at the onset of labor or during labor because a poor placenta or a hypertonic uterus deprives the fetus of oxygen. A relaxed confidence on our part, even belief that the safest and best for the baby is a "natural childbirth," is an attitude unlikely to favor the early detection of fetal distress.

Perhaps it would be well to remember that in modern society "natural selection" no longer assures perpetuation of only those best suited for reproduction. Ironic but in all probability nevertheless true, the better the obstetrics practiced in a given area, the less the chances that natural selection will assure a predominance of those women physiologically best suited to bear children in each succeeding generation. Each generation of doctors is likely to care for a greater number of women who, for one reason or another, are not likely to reproduce unless aided and supported by good obstetric care.

Summary

To summarize we would emphasize the following:

1. The umbilical cord appears quite vulnerable and accidents to the cord not infrequently account for fetal death. Reviews indicate that one fifth to one fourth of the intrapartum fetal deaths are usually ascribed to this complication.

When evidence of fetal distress leads to the discovery of a prolapsed cord the diagnosis may have been made too late to save the fetus by any means of delivery.

Vaginal examination immediately after rupture of the membranes is always advisable in an effort to discover prolapse of the cord at the earliest possible moment.

Failure to make such a precautionary exploration, with a transverse lie or a shoulder or a breech presentation, would be carelessness to a point of neglect.

2. Abnormality or dysfunction of the placenta probably account for a majority of all stillbirths, the proportion varying with the reviewer's willingness to assign all deaths due to fetal anoxia to this cause, or his belief that all such suspected causes might better be regarded as deaths due to ill-defined or unknown cause.

3. Good obstetric judgement is most important in the management of any pregnancy in which placental dysfunction is suspected. We should watch for fetal distress in every labor, but especially;

(a) When there is a history of infertility, of previous abortion, premature labor, abruption of the placenta, or an unexplained stillbirth, or whenever bleeding and abortion threaten in the first trimester or bleeding or toxemia develop in later pregnancy.

(b) Whenever in the last trimester of pregnancy, fetal growth does not seem "up to schedule." We must then decide if our calculations are a month off or if the fetus has quit growing.

(c) Whenever labor fails to begin and pregnancy seems prolonged more than 2 weeks beyond what we feel is probably a correctly estimated date of confinement. The probability of placental inadequacy is increased if the size of the uterus seems to be diminishing.

(d) Whenever rupture of the membranes reveals discoloration or a decreased amount of amniotic fluid, and particularly whenever fetal heart sounds are found to vary noticeably with uterine contractions.

4. While there are differences of opinion regarding the significance of a fetal heart rate above 160 per minute, fetal distress is *suggested* when the fetal heart rate drops below 80 per minute during uterine contractions, and *evident* if heart sounds fail to rapidly resume their formerly faster rate as each contraction diminishes.

While the risk of postmaturity is questioned by many obstetricians the risk of placental insufficiency is very real. It is recognized that the diagnosis of placental insufficiency or dysfunction may be difficult to establish. For this reason we do not suggest any routine management when placental dysfunction is suspected. We are convinced, however, that we should consider the possibility of pla-

cental deficiency in every labor. If we manage each case in which fetal distress is suspected or evident, in whatever manner seems most likely to safeguard fetal oxygenation until delivery is possible, the over-all result should certainly be better. With such overall improvement we can certainly look for a marked reduction in the number of fetal deaths ascribed to "ill-defined or unknown cause."

In conclusion, let us remember that today we see many women with a history of infertility or repeated abortion, others who have lost a child nearly at term, at term, or in the first few days of life. If we are going to assure them that they should try again, we will have to accept the burden of watching them so closely as to recognize the signs of placental inadequacy or dysfunction at whatever stage of pregnancy or labor such deficiency threatens.

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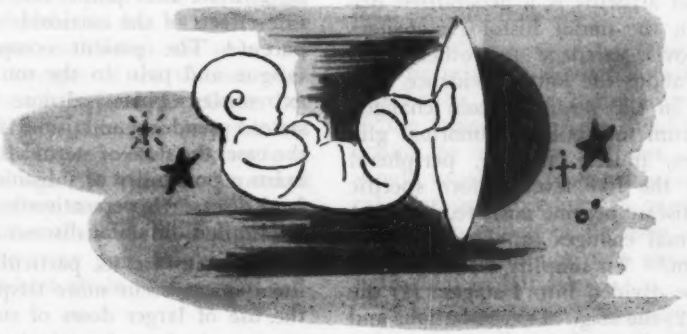

Rehabilitation in Rheumatoid Arthritis*

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The management of rheumatoid arthritis takes infinite patience on the part of the patient and the doctor. Many therapeutic tools may be used in management, both medicinal and physical, and even surgical on occasion. But care and judgment are needed in their use.

THE TREATMENT of any form of arthritis consists of an attempt to eliminate or alleviate the disability and to maintain a maximum degree of function. These aims can be accomplished through the use of rehabilitation medicine—i.e., all types of therapy available to the physician. Rusk[1] says, "The first objective of rehabilitation medicine is to eliminate the physical disability, if that is possible; the second, to reduce or alleviate the disability to the greatest extent possible; and the third, to retrain the person with a residual physical disability 'to live and to work within the limits of the disability but to the hilt of his capabilities.'" The most common arthritic disorders are those of the degenerative and rheumatoid types and gout. The treatment of rheumatoid arthritis includes the use of drugs, physical modalities, appliances, psychotherapy and all of the other facets of rehabilitation medicine.

Rheumatoid arthritis is a generalized disease in which the major histologic changes occur in synovia, cartilage and other structures in and about the joints. Evidence of it can be seen in the serum protein changes, negative calcium metabolism, abnormal glucose tolerance, muscle atrophy, peripheral neuritis, and the like, even before specific tests for the disease become positive, and long before abnormal changes can be seen on a roentgenogram.[2,3] To simplify treatment, the disease can be divided into 4 stages: (1) the acute stage; (2) the stage of exacerbations and remissions; (3) the early stage of deformity; and (4) the ankylosing stage. It may be hoped that if the proper treatment is prescribed and carried out, fewer patients will progress to stage 4, and bony ankylosis and severe deformities can be avoided. Since there are no specific remedies that will cure or arrest the disease, treatment is directed toward, (1) suppression of acute flares, (2) maintenance of function, (3) reduction of pain, (4) prevention of marked muscle atrophy and shortening, and (5) the possibility of continuing the activities of daily living.

Treatment

When the physician first sees an arthritic patient, he usually prescribes one of the many steroids. These drugs suppress pain, affording the patient a sense of security from the disease, or at least the confidence that it will not cripple him. As the patient relies on the drug to cure him, he soon discovers that larger and larger doses are required to stop the pain, and also that the course of the disease remains unaltered. At that point, one of the insidious side effects of the corticoids may become apparent.[4] The patient complains of severe fatigue and pain in the musculature of the extremities. This syndrome has been called steroid pseudorheumatism.[5] If, as is commonly the case, the dose of steroid is increased, there exists a possibility of substituting a severe-to-fatal disease (hypercortisonism) for a chronic, self-limited, nonfatal disease (arthritis).

Rheumatoid cysts, particularly in the popliteal space, occur more frequently following the use of larger doses of steroids. We have seen a number of patients who have been treated for rheumatoid flares when their main disability was pain and limitation of motion from the presence of an enlarged rheumatoid cyst. Ulceration and massive hemorrhage from the gastrointestinal tract are known to occur following the use of prednisone and predniso-

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lone.[6] Osteoporosis with compression fractures of the spine have been reported numerous times.[7] Diabetes mellitus can be made worse with the steroids and can be induced in some rheumatoid patients on large doses of the steroids.[8] The newer drugs, particularly the triamcinolone and dexamethasone, cause ecchymosis in the skin and subcutaneous tissues of the extremities.[9-11] Although no cause can be found for the bleeding tendency we have encountered instances of bleeding into the peritoneal cavity, conjunctiva, and other serous membranes. Perivasculitis and peripheral neuritis is the most severe complication we have seen and the one leading to death.[12,13]

In the treatment of rheumatoid arthritis the first step is to acquaint the patient with a few basic facts relative to the disease. The fear of being bedridden or confined to a wheel chair can readily be dispelled by telling him that about 60% of the cases burn themselves out; that 30% have exacerbations and remissions, with slight to moderate deformities; and that only 10% may advance to severe deformities or crippling. Even for patients in the latter group, it may be possible to maintain ambulation and restore function through the use of appliances and reconstructive surgery.

Patients with rheumatoid arthritis present themselves to physicians for relief of pain, the most frequent and distressing symptom of this disease. It is this symptom that causes arthritic patients to try many nostrums in their search for relief, as well as to visit quacks of all types. They must be told that pain occurs during an acute flare-up of arthritis, but that after the disease has become established, the pain may result from the ravages of the disease, even though the process is burned out. Once they understand this fact, they are less anxious than they have been to resort to steroids or other "miracle drugs." It must be impressed upon them that they must learn to live with their disease, rather than for it. The patient who can tolerate some pain rarely becomes confined to a wheel chair or becomes bedridden.

The basis of all treatment for rheumatoid arthritis is the maintenance of mobility through adequate motion, and relief of pain by means of either simple analgesics or physical therapy of the type that can be carried out at home. Despite all of the newer so-called "miracle drugs," salicylates still remain the most effective antirheumatic and analgesic agents in the treatment of arthritis. In the acute stage of the disease, when there are symptoms such as swelling, redness, pain and heat in a joint, salicylates are given orally in the form of acetylsalicylic acid. The patient is kept at bed rest, and the painful joint is immobilized in a position of comfort. This is best accomplished through the use of a Schantz wrap. Salicylates in the form of a methyl-salicylate ointment is rubbed on the skin over and near the joint, absorbent cotton is then loosely wrapped around the joint, and a three inch flannel bandage is firmly wrapped around the cotton. This type of dressing will prevent motion and relieve most of the pain. If the patient has a fever, the noninvolved joints are carried passively through a normal range of motion, and actively if there are no constitutional symptoms. These exercises are carried out at least twice a day. The dressing is removed once a day, and the involved joint is gently flexed and extended passively up to, and then slightly beyond the point of pain. After the acute symptoms subside, the patient is allowed to sit up and to exercise the noninvolved joints actively. The involved areas can be treated with hot packs, heat lamps or heating pads, and then carried through a range of motion up to, and then slightly beyond the point of pain. The patient can massage the painful areas with methyl-salicylate ointment, a procedure that helps carry out exercises for the upper extremities, keeps him occupied part of the time and helps relieve pain.

As the acute symptoms subside, graded exercises are initiated, including walking and mild calisthenics. Ten grains of acetylsalicylic acid in the form of Bufferin should be taken on arising to overcome stiffness, and the dose should usually be repeated before each physical therapy procedure to prevent excessive pain. Two tablets of Bufferin are also taken at bedtime to reduce pain, thus allowing the individual to fall asleep.

Most of the patients seeking relief of symptoms are usually in the stage of exacerbations and remission, with only slight deformities (stages 2 and 3). In that group the best results are obtained from a combination of salicylates and steroids in addition to physical therapy. Bufferin is given in varying doses until maximum results have been obtained. If the pa-

tients still have synovial swelling, marked elevation of erythrocyte sedimentation rate, slight elevation of temperature, lymphadenopathy and other signs of a true flare, then steroids can be added to the salicylates.

It is best to give these patients small, frequent doses of the corticoids, rather than 2 or 3 large doses. For example, one can give 1 mg. of the metacortisones every 3 hours around the clock (a total of 8 mg.), rather than 5 mg. tablets 3 times a day. We always instruct the patient to break the tablets in half, or if a smaller dose is prescribed, to cut the tablets into quarters with a razor blade. When the newer drugs are prescribed, they are given in 0.25 mg. (dexamethasone) or 1 mg. (triamcinolone) doses. On the basis of our accumulated experience with these drugs, we strongly recommend that smaller doses be prescribed.

It is important for the physician to bear in mind that the increased potency of the newer steroids involves added responsibility to the patient. A simple comparison between the recommended dosages of cortisone and dexamethasone should adequately illustrate this point: A 0.5 mg. tablet of dexamethasone is equivalent to a 25 mg. tablet of cortisone.

Bufferin can be given with each dose of steroid, or in between doses as needed. The dose of salicylate usually is a good indication of the effectiveness of the steroid. As soon as maximum results have been obtained, one dose of the steroid is eliminated at a time. An attempt is always made to maintain the patient on the smallest possible dose of steroid, increasing and decreasing the salicylates to meet the stress of daily living.

The patients, while receiving antirheumatic drugs, are at first kept at bed rest and given regulated exercise. As the acute phase subsides the period of exercise is increased until the patient is allowed up most of the day. Even then definite periods of bed rest should be prescribed. As soon as possible, even when the patient is at bed rest, he is taught how best to carry out the activities of daily living. These consist of washing the face, brushing the teeth, combing the hair, buttoning the pajama coat, cutting the food and feeding themselves, etc. Often, hand deformities necessitate enlarging the toothbrush handle or the grip on a rat-tail comb, by wrapping it in foam rubber and fastening the rubber with adhesive tape. Oval grips can be made of plaster of Paris or thin strips of aluminum, and to these one can affix pencils, pens, knives, forks or spoons. All appliances used to assist or to reteach the activities of daily living can be bought at moderate prices.[14]

Heat or some other modality may be used to relax the muscles and alleviate some of the pain before a joint is exercised. One of the simplest methods of transferring heat to the hands is the paraffin bath. All that is needed is a double boiler (rice boiler) and a supply of paraffin, both of which can be found in the average home. Before the hands are immersed in the warm paraffin, they are coated with lanolin or coconut butter. This allows the paraffin to be peeled off the hands without pulling the small hairs.

Hot packs are useful over shoulders or knees, for the woolen material that is used for this purpose can be moulded about the irregular surfaces. Heat lamps or electric pads can also be used, but if they are not watched carefully, they may cause blistering or minor burns. After heat has been applied for about 20 minutes, the affected part is carried through a range of motion. To strengthen weak muscles, the part is moved against resistance. This can be accomplished with a small pulley and a length of rope. A weight is tied to one end of the rope and the other end is tied lightly around the ankle or held in the hand. With this simple equipment, every type of motion can be carried out, such as flexion, extension, adduction, and abduction. At first a weight of only 0.5 to 1.0 pound should be used, and as improvement is noted larger and larger ones can be employed, depending upon the patient's age, sex and severity of disease.

Exercises carried out in the home or in the place of the patient's employment are more effective than those performed in a clinic or hospital. A young woman can obtain better exercise of the fingers or wrists by using a typewriter or operating one of the many electric bookkeeping machines than by manipulating a rope, pulley and weight gadget such as has been described. A housewife can exercise her fingers, wrists, elbows and other joints adequately by peeling potatoes, grating carrots, dusting the furniture, rocking in a chair or going through others of her accustomed motions. Heat can be obtained in a bathtub of warm water, and while the patient sits im-

mersed, a part of the effect of gravity is removed from his limbs, and he can perform exercises with minimal pain.

The arthritic farmer can warm his hands in tepid water and then milk the cows to maintain strength and dexterity in his fingers. Shoulder exercises can be graded by moving a pump handle up and down at a definite rhythm and speed. Knee and hip exercises can be done by moving the pedal of a grindstone or by working in the garden. Thus, the home or place of employment provides ideal areas in which to carry out numerous types of exercises, all of which will maintain strength and mobility, and prevent marked atrophy and ankylosis.

Every effort should be made to prevent deformities of arthritic joints. To alleviate pain, the patient tends to keep the involved joints in partial flexion, especially at night. This is usually the first step in the inevitable flexion contracture seen too often in these patients. They should sleep on a bed that does not sag, and should keep the joints in full extension. Pillows should never be placed under the knees. A small pillow should be used to prevent flexion contractures of the neck. Night splints made of plaster of Paris, aluminum or plastics can be applied to prevent ulnar deviation and marked flexion contracture of the wrist. Placing the hands beneath the head on first going to bed will maintain motion of the shoulders. Chewing gum often prevents partial ankylosis of the temporomandibular joint. Pillows, sand bags and footboards are used to prevent increasing flexion of joints of the lower extremities. Patients should be warned against using sloppy bedroom slippers, particularly when first starting to walk. Callouses should be trimmed properly, as should corns, and shoes should be well fitted. If necessary, the shoes should be fitted with metatarsal bars, heel pads or wedges, and soft felt pads under the instep.

The proper diet for arthritic patients has been the subject of many dissertations. The only diet that is useful is one that provides the individual with the necessary amounts of proteins, carbohydrates, fats, minerals and vitamins, and that contains enough calories to prevent a gain in weight. The use of colonic irrigation and the giving of continuous doses of laxatives should be condemned. The average arthritic has little or no constipation, and the use of irrigations and laxatives can soon lead to an irritable bowel and a very irritable patient. Home exercisors as special bicycles or bar bells, should not be used, for they intensify the joint damage.

Climate is another modality offered patients as a cure-all. Many an individual chases the pot of gold at the end of the rainbow, only to find that home is the best environment for his illness. States blessed with sunny climates have just as many arthritics as states in the midwest.

Spa therapy for the treatment of rheumatoid arthritis has been neglected in this country. In Europe treatment at spas or health resorts has become very popular as social security agencies and insurance companies send patients to these places in greater numbers each year. The method of treatment at these health resorts differs from the American method in that patients are given complete medical rehabilitation in a subtle manner. Instead of admitting them to a hospital ward or room where the entertainment is primarily a loud blaring radio playing "rock 'n roll" music or a television set depicting a "soap opera," the individual going to a European health resort uses the sanatorium or hotel bed merely as a place to rest. Most of the people are referred to the spa by their local physician and after careful examination, including the routine laboratory tests, the necessary treatment is prescribed. Treatment at these spas, includes walking (graded exercises) in beautiful parks, listening to symphony orchestras, receiving physical therapy in the form of baths of hot thermal water, diets are served in clean quiet and oftentimes beautifully decorated dining halls and definite periods of rest are enforced following the exercises or baths. Most of the communities in which the spas are located have municipal regulations preventing trucks or motor bikes, from entering the area after 5 p.m. In the evening most of the clients attend concerts, lectures, or movies after which they are ready for bed. By catering to the 5 senses the habits are well regulated, and at the end of a 3 week period the arthritic is able to reduce the dose of drugs, is mentally more relaxed, has a better range of motion of the joints and can return to his usual occupation. There are a few places in this country where spa therapy is

given, but unfortunately the average American physician is not aware of this most excellent form of therapy.

Our final discussion involves the ankylosing stage (stage 4). At present much can be done for these cripples through surgical rehabilitation. Before any such procedures are attempted, it is necessary to determine whether the patient has true dense-fibrous or bony ankylosis, or whether he is bedridden because no attempt has been made to ambulate him. Again, the individual must be shown and convinced that the pain is not caused by the acuteness of the disease, but by the damages resulting from it. Some of these people can be ambulated through the use of psychotherapy, various types of physical therapy, braces and walkers. Surgical procedures may then help salvage more of these individuals. There are a number of surgical procedures that can be carried out early in the disease to prevent further deformities. Recurring fluid in the knee joint, despite frequent aspirations and instillation of hydrocortisone, can be slowed down or stopped by synovectomy. Surgery on the hand may prevent excessive ulnar deviation and maintain function of the fingers.

Summary

Treatment of the arthritic patient is most effective when he is given a thorough explanation of the natural history of the disease by his doctor. Sufficient time must be spent with the patient to achieve reassurance and psychotherapy may be used to dispel the fear of severe crippling.

The aim of all treatment is to maintain mobility and function, to enable the patient to remain self-sufficient. Pain is the most common and most distressing symptom of the disease.

The drug of choice is acetylsalicylic acid. When necessary, corticoids can be a valuable supplement, but they should be used with caution.

It is important to prescribe periods of rest to achieve optimum mobility in the arthritic patient. Various types of heat will help maintain function and reduce pain. Exercises that can be carried out in the home or place of employment will prevent marked deformities, marked ankylosis, some of the muscle atrophy, and will help strengthen the muscles.

A few of the marked deformities of the hands and feet can be prevented by early surgical procedures. In cases of crippling deformities, surgical rehabilitation may help restore some functions.

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Discussion (Abstract)

Dr. Edward M. Krusen, Dallas, Tex. Dr. Paul's paper is a very effective practical outline of the long range treatment of rheumatoid arthritis. He has stressed the prognosis of rheumatoid arthritis, pitfalls of steroid therapy and also the procedures the patient can be taught to do for himself which are essential in treatment.

There are a few points which I believe need clarification. In our experience peripheral neuritis can occur without severe perivasculitis, with and without steroid therapy, and without it being the most severe complication and the one leading to death.

Also, I assume that if the Schantz wrap is removed once a day and exercises are carried out at least twice a day, no attempt is made to get full range on the other occasions when the wrap is still on the patient.

Also, I feel there are certain patients in stage one or the acute stage who also need steroids although I agree with Dr. Paul that all of us are all too prone to start steroids too early and often unnecessarily. We have also found that ordinary salicylates or enteric-coated aspirin can be used in many patients instead of Bufferin.

Ordinary activities are certainly to be encouraged in rheumatoid patients if done within tolerance. There is a place we feel for specific strengthening exercises and often the best place to teach the patient such exercises is in a clinic or hospital. It is not practical to continue it indefinitely.

Primary Neoplasms of the Ureter*

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The clinical picture of this uncommon tumor is considered. The difficulties in diagnosis and the place of radiologic study are thoroughly discussed. Therapeutic management remains an individual matter dependent upon the case.

PRIMARY NEOPLASMS of the ureter are relatively rare tumors and are among the most malignant lesions of the urinary tract. The thin wall of the ureter offers a limited barrier through which the tumor must grow before becoming an advance lesion. Fortunately, by use of modern urologic and radiologic methods, these tumors may be diagnosed at a relatively early stage in their development. Ureteral tumors of limited growth may be adequately treated. It is important, therefore, that physicians be on the alert for the occasional case of primary malignant ureteral tumor.

This report concerns the 15 cases encountered at the Ochsner Clinic during the past 12 years. Study of these cases and review of some of the reports in the literature have convinced us that proper diagnosis demands the close cooperation of the radiologist and urologist, and that adequate therapy demands aggressive, modern urologic surgical measures.

Review of Literature

Most historical reviews credit the first proved case of primary ureteral neoplasm to Wising and Blix in the German literature, in 1878. Davy reported the first such case in the English literature in 1884. Not until 1902 did Albarran, in France, record the first case in which a correct preoperative diagnosis was made by cystoscopic visualization of the tumor protruding from the ureter. After that, occasional cases were recorded and Aschner,[1] in the first large general review of these tumors in 1922, could find reports of only 47 cases. The possibility of diagnosis improved greatly after means were devised to visualize the mucosal contours of the upper urinary tract by radiographic means. In 1924, Crance and Knickerbocker[2] recorded the first case of a ureteral tumor clearly demonstrated by urographic study. As diagnostic facilities have improved and become more widespread, and as the general population and the average age have increased, reports of these tumors have become more frequent. Lazarus,[3] in 1934, listed 71 cases, a review by Scott,[4] in 1943, mentioned 182 cases, and a more recent extensive review by Abeshouse[5] indicates a total of 454 cases of malignant and 138 benign ureteral tumors through June, 1954.

Pathologic Varieties

The epithelial lining of the ureter is identical to that found in the renal pelvis and the bladder. It is a transitional stratified epithelium occasionally referred to as "urothelium." We do not propose to consider the pathologic features in detail, but we should like to quote some words of the pathologist, Willis:[6] ". . . although it is customary, and for clinical purposes useful, to distinguish between benign papillomas and carcinomas of the urinary tract epithelium, it is impossible to make any real pathological distinction between them. Here more than any other situation, there occur tumours showing every possible gradation and every possible sequence from solitary, highly organized non-invasive papilloma to disorderly invasive carcinoma."

Ureteral tumors may be single or multiple, polypoid or sessile, ulcerating or nonulcerating, and infiltrating or noninfiltrating (Fig. 1). These features may be present in any sequence or in any combination. The growth in the ureter may or may not produce obstruction to the flow of urine; and, with this, varying degrees of hydronephrosis may be present (Fig. 2). Metastatic lesions may

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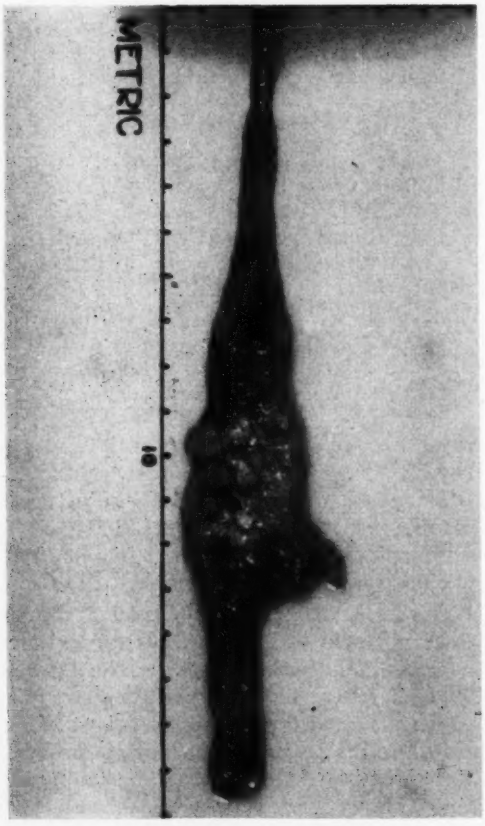
occur. Direct invasion through the thin wall of the ureter indicates a poor prognosis.

Subdivision of these neoplasms may be arbitrary to some extent. The classification devised by Whitlock and co-workers[7] seems practical. Their three chief divisions are,—(1) papillary carcinoma, (2) papillary and infiltrating carcinoma, and (3) nonpapillary infiltrating carcinoma. The cell type, transitional or squamous, may be appended. Microscopic evidence of invasion of lymphatic vessels or veins is considered important and carries a grave prognostic significance. Whitlock and co-workers pointed out that "papillary" is a descriptive term based on microscopic study and not gross appraisal of the tumor. The distribution of our 15 cases according to Whitlock and co-workers' types is shown in Table 1.

Papillary tumors are frequently multiple.

FIG. 1



Polypoid ureteral neoplasm.

FIG. 2

Obstructing ureteral neoplasm has resulted in severe hydronephrosis.

Coexistence of tumors in the renal pelvis or bladder is not rare. Whether these are metastatic transplants or multifocal tumors is a debatable point. The important fact is that the urothelium in all areas is exposed to any carcinogenic agent that may be in the urine. The possibility of multiple lesions, therefore, must be kept in mind.

TABLE 1

DISTRIBUTION OF 15 CASES OF PRIMARY URETERAL NEOPLASMS ACCORDING TO PATHOLOGIC TYPE

Pathologic Type	*Transitional Cell*	*Squamous Cell*	*Total*
Papillary carcinoma	5	1	6
Papillary and infiltrating carcinoma	6	1	7
Nonpapillary infiltrating carcinoma	1	0	1
Adenocarcinoma	—	—	1
Total			15

Age and Sex Incidence

The usual patient is elderly, Abeshouse[5] having set the percentage of patients older than 50 years at 85. The average age of our 15 patients was 61 years, the range being from 41 to 77 years.

These tumors are found about twice as often in the male as in the female sex. Ten of our patients were males and 5 females.

Clinical Manifestations

Clinical manifestations traditionally include the triad of hematuria, pain and abdominal mass. In our 15 patients, 12 had hematuria, 8 pain, and 2 a mass. The finding of an abdominal mass should not be anticipated and pain is much less frequent and less clinically significant than the cardinal finding of hematuria. Other symptoms (as frequency, nausea, weakness) are infrequent and of no assistance in detection.

The importance of discovering gross or microscopic amounts of blood in the urine cannot be overstated. Patients with hematuria require thorough combined radiologic and urologic appraisal. The hematuria that occurs in patients with ureteral neoplasms follows no particular pattern.[4] The quantity may vary from microscopic to massive amounts; the urine may or may not contain blood clots; the hematuria may or may not be painful; and the bleeding may seem to be periodic but usually occurs in a completely irregular sequence of varying duration and at varying intervals of time. Both Scott[4] and Twinem[8] reported hematuria in 70% of their patients.

According to Moore[9] some type of pain occurs in 60% of cases. He described pain of 3 types: ureteric colic from obstructive features of the tumor or clots of blood; renal ache produced by distension of the ureter, renal pelvis or calyces; and referred pain due to involvement of surrounding structures.

In instances in which a mass can be felt, it is generally a hydronephrotic kidney that is being palpated. On rare occasions the primary tumor of the ureter may itself be palpable. In general, however, the tumor is too small to be felt through the abdominal wall. Occasionally, a tumor lying low in the ureter may be felt by vaginal or rectal examination. In one of our patients, a tumor in the middle third of the right ureter was discovered by the surgeon who was palpating the retroperitoneal areas at the time of cholecystectomy for acute calculous cholecystitis.

Associated stones in the urinary tract occur occasionally and must not divert attention from full evaluation of patients with hematuria.

Roentgenologic Observations

Plain Roentgenogram.

Roentgenography of the kidney, ureter and bladder gives limited but useful information in some cases (Table 2). The hydronephrosis that may be present in patients with obstruction produces a renal shadow that is larger than normal. In such cases, further examinations are indicated to determine the reason for this enlargement.

Opaque urinary calculi are said to occur in 6 to 15% of primary ureteral tumors.[5,10] Discovery of urinary stones in any patient should lead to thorough urologic study. Abeshouse's[5] report of a case of a papilloma covered with calcium that mimicked an opaque stone is of interest.

It is unlikely that the primary shadow of the ureteral neoplasm will be seen, as the tumor usually is relatively small and the shadows of adjacent soft tissues provide no contrast in density. Superimposed shadows of the bony structures serve only to confuse the appearance. If a ureteral tumor is discovered, however, it is important that the lungs and the bones be studied for possible metastatic disease. In cases coming to necropsy Willis[6] reported that one third had lymphatic metastasis and one third had blood-borne metastasis. Lazarus and Marks[10] reported metastatic foci in bones in 12.3% of cases and in the lungs in 7 per cent.

Excretory Urography.

Radiographic visualization of the ureter after renal excretion of intravenously injected iodide compounds has become a standard means of urographic examination. Use of currently available agents, as Hypaque, per-

TABLE 2

ROENTGENOGRAPHIC OBSERVATIONS IN 15 CASES OF PRIMARY URETERAL NEOPLASMS

Finding	*Cases*
Normal	11
Hydronephrosis	3
Associated renal calculus	1

mits satisfactory demonstration of the entire course of the ureter in many patients. Realization of best results requires proper preparation of the patient for the examination, lower abdominal compression to assure adequate filling of the upper ureters, films made with the patient in the erect position to demonstrate the lower segments, multiple films to show constancy of abnormalities, precise radiographic technic, and prompt inspection of roentgenograms to allow variation of examination as individual cases require. Even with such meticulous technic, there is at times poor delineation of the lower third of the ureter, where the greatest number of primary ureteral tumors is found. Care must be exercised in interpretation of urograms in which visualization is not complete, particularly in symptomatic patients.

The roentgenographic pattern of abnormal changes progresses as the tumor becomes larger and increasingly obstructs the ureteral lumen (Table 3).

1. *Regional Narrowing of Ureter.* As the size of the epithelial mass increases, whether this be an intraluminal polypoid growth or intramural infiltrating neoplasm, the effective lumen is diminished in size. As the contrast medium passes through this zone, the lumen does not fill up to the normal caliber that is seen in other segments of the ureter. This segmental narrowing should be the initial roentgenographic appearance of disease. Diagnosis at this stage is difficult, however, because the ureter normally shows a variable diameter because of its peristaltic activity. Incomplete filling of the ureter is so frequent that areas mimicking stenosis are common. Consequently, it is hazardous to make a diagnosis of definite ureteral narrowing unless there are associated abnormalities.

2. *Marginal Filling Defect.* If the margin of the stenotic area is formed by an intraluminal polypoid mass, it will protrude into the column of opaque medium with a sharply defined edge. This irregular, radiolucent "filling defect" then occupies a portion of what should be the ureteral lumen.

TABLE 3

EXCRETORY UROGRAPHIC OBSERVATIONS IN 15 CASES OF PRIMARY NEOPLASMS OF THE URETER

Finding	*Cases*
Hydronephrosis	6
Unilateral nonvisualization (Complete ureteral obstruction)	5
Dilatation of ureter	3
Regional narrowing of ureter	3
Marginal filling defect	2
Multiple lesions	1
Localized calyceal deformity (Inflammatory disease)	1

3. *Dilatation of Ureter.* If an area of narrowing is associated with dilatation of the ureter above the lesion, one must suspect obstructing disease and not merely spasm of the ureter. Braasch and Emmett[11] stressed this and pointed out that ureterectasis may be the initial urographic indication of obstruction from a tumor. Others have pointed out the ureters should not be persistently filled along their whole course in excretory studies, and when an unusually well-filled ureter is discovered, obstruction should be suspected.

4. *Hydronephrosis.* Dilatation of the renal pelvis and calyces may follow or precede the development of hydro-ureter. Hydronephrosis may be discovered and the causes for it remain obscure, because the ureteral lesion is not revealed by the study. This is a situation when the contrast medium is too diluted in the hydro-ureter or when the diseased segment is not visualized. Twinem[8] pointed out that cases of unilateral hydronephrosis without apparent cause should arouse suspicion of possible ureteral tumor.

5. *Complete Ureteral Obstruction.* Continued growth of the neoplasm may eventually produce complete obstruction to the passage of liquid through the lumen. This results in cessation of renal excretory function which is manifest in urographic studies as nonvisualization of the calyceal system after injection of urographic medium (Fig. 3). That this happens relatively often is indicated by the report of Holmes[12] of 10 cases of nonvisualization among 14 patients, an incidence of 71 per cent. Discovery of a nonfunctioning kidney by excretory urography should lead to suspicion of ureteral neoplasm, especially if the patient complains of hematuria and if the plain roentgenograms show no evidence of a radiopaque ureteral stone.

6. *Unusual Complications.* Manifestation of intussusception of the ureter or development of a fistula at the site of the neoplasm is rarely visualized by excretory urograms.

7. *Multiple Lesions.* Multiple lesions may occur. Evidence of a tumor in the bladder or renal pelvis should lead one to

FIG. 3

Left kidney shows no function during excretory urography.

examine the ureter carefully.[13] Finding multiple filling defects maintaining a constancy in appearance and location in the urinary tract should suggest a diagnosis of multiple papillary tumors.

Retrograde Ureteropyelography.

A combined cystoscopic and radiologic examination provides maximum information and is usually mandatory, because excretory urograms are rarely completely diagnostic. Circumstances may prevent complete passage of the ureteral catheter, but injection of contrast material into the lower ureteral segment may result in sufficient visualization to localize a tumor or give considerable information about it. A Braasch bulb type of instrument to obtain a diagnostic ureteropyelogram should be employed routinely in patients suspected of having ureteral tumors. Technical finesse and persistence are important virtues in retrograde study in unusual cases. A flexible radiographic technic, likewise, results in better visualization of a larger percentage of lesions than any stereotyped method of obtaining films. Pyeloureterograms may show the same types of change described in the excretory urogram but visualization is usually superior (Table 4).

TABLE 4

RETROGRADE URETEROPYELOGRAPHIC FINDINGS IN 15 CASES OF PRIMARY NEOPLASMS OF THE URETER

Finding	*Cases*
Localization of neoplasm	11
Regional narrowing of ureter	7
Marginal filling defect	7
Dilatation of ureter above lesion	6
Hydronephrosis	5
Ureteral obstruction	4
Inferior margin of ureteral tumor	4
Intraluminal polypoid mass	3
Dilatation of ureter below lesion	2
Attempt unsuccessful	2
Multiple or metastatic tumors	1

1. *Regional Narrowing of Ureter.* Identification of persistent slight luminal stenosis

FIG. 4

Retrograde ureteropyelography shows severe hydronephrosis of left kidney and stenosing neoplasm of left ureter at sacral level. (Same case as Fig. 2.)

is much more certain when based upon retrograde studies (Fig. 4). Not only may the total course of the ureter be demonstrated, but the ureteral distention produced by retrograde filling makes the narrowed area stand out by comparison. Irregular narrowing is particularly suggestive of neoplasm.

2. *Marginal Filling Defect.* In addition to making the regional stenosis more apparent, the distention of the normal ureter above or below the lesion provides a better opportunity to see the margins of the tumor. Nodular edges or a sharply defined border suggests tumor rather than benign stricture.

3. *Dilatation of Ureter Above Lesion.* The usual obstructive lesion produces ureteral dilatation. If contrast material can be introduced into the segment above the neoplasm, the degree of ureterectasis may be established.

4. *Dilatation of Ureter Below the Lesion.* Ureteral dilatation below the neoplasm is common. This may be the result of mechanical overdistention of the ureter by retrograde injection, or may indicate that intussusception, similar to that described by Hunner,[14] occurs more frequently than is usually appreciated.

5. *Intraluminal Polypoid Mass.* A tumor growing from the epithelial surface as a polyp or a protruding nodular mass produces a typical filling defect in the column of contrast material which is used to fill the ureter in retrograde studies (Fig. 5). The size and shape of the defect are determined by the gross morphologic characteristics of the tumor. The appearance of the lesion may vary from a single pedunculated polyp, which is seen as a small radiolucent shadow, to an extensive irregular mass which presents bizarre contours and crevices when outlined by radiopaque medium. Holmes[12] reported one in which the pattern of filling defects was reminiscent of the trabeculations seen in a giant cell tumor.

6. *Hydronephrosis.* A long standing, partially obstructing ureteral neoplasm may result in varying degrees of hydronephrosis. Mild changes of calyceal clubbing are better determined by excretory urograms, because the pressure of retrograde injection frequently leads to some blunting of the margins of the calyces. If the hydronephrosis is more pronounced and renal function is sufficiently impaired to prevent satisfactory excretory study, retrograde pyeloureterography is useful in assessing the renal status.

FIG. 5

Retrograde ureteropyelogram shows polypoid and partially obstructing neoplasm in lower right ureter.

7. *Ureteral Obstruction.* As the degree of ureteral obstruction increases, it may not be possible to pass a catheter up the ureter. Even at this stage, however, fluids may pass and sufficient contrast medium may be introduced to give diagnostic information (Fig. 6). When the obstruction becomes complete, retrograde injection no longer gives positive information about the ureter above the site of obstruction.

8. *Inferior Margin of Ureteral Lesion.* Even though the contrast medium may not pass an obstructing lesion, it may give valuable information. Widening or cupping of the ureter, nodularity of the end of the opaque column, or some irregularity of one of the edges of the column should suggest possible neoplastic obstruction.

9. *Localization of the Neoplasm.* Retrograde visualization is useful in localizing a

FIG. 6

Neoplasm in left ureter prevents passage of ureteral catheter, but contrast medium reveals a tumor that narrows lumen and has shelving borders.

tumor and in determining its extent. Even if only the inferior border is visualized, it may be possible to define the extent of the neoplasm, by superimposing retrograde and excretory urograms.[12] The former determines the lower edge and the latter indicates the superior extent of the tumor.

10. *Unusual Position or Coiling of Catheter.* Coiling of the catheter in the ureter below the neoplasm or perforation of the diseased ureter is infrequent. The pattern of extravasation of contrast medium is diagnostic.[12]

11. *Fistulous Tract.* In advanced neoplasms, extension of the growth may involve adjacent tissues or organs. Fistulas involving the intestine and vagina have been described.[9]

12. *Multiple or Metastatic Tumors.* Multiple lesions should be more efficiently demonstrated by retrograde studies, because of more complete visualization of the ureter.

Differential Diagnostic Problems.

Roentgenologic identification of ureteral tumors is not a simple exercise from the standpoint of obtaining films and interpreting them (Table 5). Stress is laid upon the necessity for satisfactory roentgenograms. It is widely accepted that more errors in urographic diagnosis result from interpretation of inadequate excretory urograms than from any other single cause. Poor technical factors and improper film processing produce inadequate roentgenograms. Superimposed fecal and air shadows of the intestinal tract may obscure the area of disease. Muscular contractions of the ureter may mimic stenotic lesions. Developmental anomalies and physiologic variations may confuse the unwary. Air bubbles introduced during insertion of retrograde catheters are usually small, rounded, multiple radiolucent shadows and move in position enough to be confidently identified. Blood clots may produce rounded, elongated or bizarre ureteral defects but usually do not produce ureterectasis, rarely prevent retrograde catheterization, and are not as constant in position or appearance in multiple examinations as are tumors. Inflammatory lesions of the ureter are rarely as localized as neoplasms, do not show polypoid defects, and the associated clinical findings and primary involvement of the kidney generally permit differentiation.

Ureteritis cystica is seen as smaller, scattered multiple lesions often associated with cystitis cystica. Benign stricture is more often encountered in a younger age group, is less often accompanied by hematuria, presents stenosis with smooth margins and without intraluminal filling defects, and occurs at the origin or termination of the ureter.[15] Carcinoma of the bladder usually can be differentiated by cystoscopic appraisal.

In urographic diagnosis, as in other roentgenographic examinations, the importance of sequential changes during periods of time is frequently not appreciated. One examination may give equivocal evidence regarding the presence of disease. If current roentgenograms can be compared with those

TABLE 5

DIFFERENTIAL RADIOGRAPHIC DIAGNOSES IN PRIMARY NEOPLASMS OF THE URETER

Incomplete visualization of ureter.
Superimposed fecal or air shadows.
Physiologic muscular contraction.
Developmental anomaly.
Compression from adjacent mass.
Ureteral calculus.
Benign stricture.
Blood clot.
Inflammatory disease.
Ureteritis cystica.
Air bubbles.

of a previous study, the diagnosis may be obvious. The reason is that minor individual abnormalities become more apparent. When available, previous films should be obtained for comparison.

Cystoscopic Observations

Cystoscopic visualization of the bladder and ureteral orifices is imperative in all patients whose clinical, urinary, or prior roentgenographic findings suggest the possibility of ureteral neoplasms. As a general rule, excretory urography will have preceded diagnostic cystoscopy. It is highly desirable that the examination be performed in surroundings which permit retrograde pyeloureterographic study in conjunction with cystoscopic procedure. Only by combined examination can the diagnostic study be complete when ureteral disease is suspected.

1. *Normal Cystoscopic Study.* As shown in table 6, cystoscopic visualization alone gave negative results in 4 of our 15 cases. Important points are that results of cystoscopy may be negative and that prompt radiographic studies must be undertaken.

2. *No Urine or Dye from One Ureter.* Detection of urine issuing from a ureter may be difficult. This may not be necessary if a preceding urogram has been done, but it is possible to study this by injecting a dye (such as indigo carmine) intravenously and watching for its excretion from the ureter. Failure of visualization on one side while the other side is normal may be an important clue to disease of the upper tract.

3. *Blood from Ureteral Orifice.* The importance of seeing bloody efflux from one ureteral orifice cannot be overstated. This finding alone demands complete investigation and treatment.

TABLE 6

CYSTOSCOPIC FINDINGS IN 15 CASES OF PRIMARY NEOPLASMS OF THE URETER

Finding	*Cases*
Intra-ureteral obstruction to passage of catheter	5
Bladder changes at ureteral orifice (Elevation, gaping orifice, edema, congestion)	4
Normal	4
Blood from ureteral orifice	2
Papillary tumor at ureteral orifice	2
Obstruction at ureterovesical orifice	2
Increased bleeding after ureteral catheterization	2
Associated papillary tumor of bladder	2
Positive cytologic study (on collected urine)	1

4. *Papillary Tumor at the Ureteral Orifice.* Direct positive diagnosis can be made when the tumor is seen protruding from the orifice of the ureter. This occurred in 2 of our cases. Twinem[8] reported it in 4 of 20 cases and O'Conor[13] in 8 of 33 cases, whereas Foord and Ferrier[16] indicated that it may occur in 30% of cases.

5. *Bladder Changes at Ureteral Orifice.* Although less striking than visualization of the tumor, some abnormalities may suggest possible tumor. These include, (a) elevation of the intramural portion of the ureter, (b) gaping orifice of one ureter, (c) edema or congestion about one orifice, or (d) localized changes of cystitis cystica.[5]

6. *Obstruction of Ureterovesical Orifice.* A neoplasm arising from the ureter at the orifice or a polypoid mass filling the lower ureter may produce complete obstruction. No urine issues from the ureter. Catheterization from below is unsuccessful.

7. *Intra-ureteral Obstruction to Passage of Catheter.* When a tumor is present above the level of the orifice, it may be possible to insert a catheter into the ureter but the passage is blocked above. While localization may be judged in some degree by the length of the catheter which could be introduced, precise information depends on radiographic visualization after instillation of contrast medium.

8. *Increased Bleeding after Ureteral Catheterization.* Trauma to the neoplasm from ureteral catheterization may result in increased ureteral bleeding (Chevassu-Mock sign). This occurred in 2 of our patients.

9. *Clear Urine Above Lesion.* Drainage of clear urine when the catheter passes above a partial obstruction is known as Marion's sign. It depends upon the fact that the epithelial lining above the tumor is normal and does not contain blood, whereas the neoplasm may be introducing blood into the urine which passes it and is collected in the urinary tract below. This has been reported occasionally but was not noticed in any of our cases.

10. *Associated Papillary Tumor in Bladder.* Because of the tendency of papillary tumors to metastasize to, or develop in the urothelium below a primary neoplasm, associated tumors of the bladder may be seen. Such a tumor was present in 2 of our 15 cases.

O'Conor[13] stressed that the finding of papillary tumor of the bladder must lead one to suspect a tumor higher in the urinary tract.

11. *Collection of Urine for Cytologic Study.* By ureteral catheterization, urine may be collected for cytologic study by Papanicolaou stain. Twinem[8] reported discovery of suspicious cells in 2 of 4 patients in whom this examination was done.

Treatment

Surgical excision has been proved to have long-term benefit in ureteral tumors. In 1943, Scott[4] listed about 50 different surgical procedures that had been recorded for ureteral tumors up to that time. The modern concept[5,10,15,17] is that radical nephro-ureterectomy should be done, including a cuff of bladder about the ureteral orifice. Eight patients had nephro-ureterectomy without removal of a bladder cuff (Table 7); the average length of survival has been slightly longer than 2 years, but 3 are still alive. In the 7 patients who had nephro-ureterectomy with cuff excision, the average survival has been more than 5 years, and 3 are still alive. In cases of a solitary kidney, local excision with end-to-end anastomosis or replacement of the ureter by a segment of ileum should be done.

The effect of radiation therapy is difficult to assess. The number of patients treated with roentgenotherapy has been small.[18] There has been no accepted standardization of radiotherapeutic technic. Cook and Counseller[19] recommended postoperative radiation in all cases. Others have used irradiation only if it seemed that all of the tumor was not excised or if recurrence developed rapidly after excision. Such cases comprise, in general, a group with less favorable prognosis at the outset of therapy, and cannot be directly compared with cases in which the neoplasm was less extensive and complete excision seemed assured at operation.

We believe that radiation therapy does have a place in the treatment of these neoplasms. If the tumor is nonresectable or operation is contraindicated, there can be little objection to radiation as a method to relieve pain, to assist in hemostasis, and to attempt temporary restraint of the tumor's growth.[20] If the surgeon believes that some gross tumor remained after attempted excision, or if contamination due to spillage of necrotic tumor occurred, postoperative radiation seems advisable in an attempt to hinder further growth of the tumor.

The most debatable situation occurs after apparent successful excision of the tumor. Should the patient receive postoperative radiotherapy? Many urologists would employ radiation only after recurrence is manifest. Why employ irradiation postoperatively in all patients when only some of them will later manifest metastases? Why subject all of these patients to the expense, the discomfort, and an occasional severe reaction? So runs this line of thought. On the other hand, many radiologists would prefer to treat all patients as soon as they recover from the operation. The philosophy upon which this opinion is based is that the recurrence rate is fairly high and is usually local; that it comes from cells present in the tissue before operation, or spilled in the process of operating; and that it is easier to devitalize or destroy the relatively few cells at this time than it is to control a much more massive volume of tumor which has developed by the time these cells have multiplied, spread, and produced gross recurrence. Why wait until an unfavorable stage when it is possible to attack the disease earlier?

TABLE 7

RESULTS OF NEPHRO-URETERECTOMY IN 15 CASES OF PRIMARY URETERAL NEOPLASMS

Treatment	*Cases*	*5 Year Survival*	*Still Living*	*Average Survival (Years)*	*Postoperative X-ray*	
					Cases	*5 Year Survival*
Without cuff of bladder	8*	1**	2	2.2	2	0
With cuff of bladder	7	3	4	5.3	4	2***

*One not followed.
**Died in 6th postoperative year, at age of 86 years, with recurrence.
***One died in 9th postoperative year, at age of 78 years, of cardiac disease.

Conclusion

These are the horns of this therapeutic dilemma. We do not believe that a definite answer is possible in the state of our present knowledge. Until there is, each case will have to be individualized, and we think that each should be evaluated with operation and possible radiotherapy in mind. In the treatment of ureteral tumors, as in many other types of cancer, progressive improvement of mortality rates may depend upon cooperation and mutual assistance of the urologist and the radiologist. Future discoveries may add new methods for treatment of disease, but it seems likely that treatment of the individual patient will always demand coordinated endeavor by thoughtful and understanding physicians.

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A New Treatment of Radio-Ulnar Synostosis*

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The authors offer a means of avoiding, or treating, if it has occurred, synostosis between the radius and ulna. This may be a difficult complication of fracture to treat.

Synostosis occurring at the proximal end of the radius and ulna may be congenital or traumatic, but for the purposes of this discussion only the traumatic radio-ulnar synostosis will be considered. Any fracture occurring in the proximal ends of the radius and ulna (most particularly in the Monteggia type of fracture) in which sufficient disruption of soft parts has occurred to allow hemorrhage from one fracture site to pass into another, there exists the prerequisites for a potential radio-ulnar synostosis. This condition, however, may occur with fractures of the proximal end of the radius only, without fracture of the ulna. Once the synostosis has occurred the physician is faced with a problem of the first magnitude.

With the increasing incidence of elbow injuries there has been a relative increase in post-traumatic synostoses between the head of the radius and the ulna. This complication is relatively uncommon (exact figures have never been published) and in our experience it has been very infrequent. In one of the hospitals of our community there were no cases reported prior to 1949, and since that time only 7 cases. In another large hospital only one case has been signed out with this diagnosis. In this office, since 1946, we have had only 5 cases.

Methods of Treatment

There is very little written in the literature on this subject and the standard texts dismiss the subject with little more than a paragraph, despite the serious disability which it imposes upon the individual and the difficulties encountered in its treatment.[1] The recommended treatment in the past has been the use of fascial type arthroplasties or the interposition of soft tissue, but Kelikian and Dumanian[2] have met the problem by the insertion of a metallic swivel in the midshaft of the radius with no attempt to treat the synostosis directly. More recently Freeman[3] has presented an impressive series of cases using an inert plastic material with seemingly excellent results.

The close proximity of the radius to the ulna in this area is undoubtedly the prime factor in the development of a synostosis as mentioned above. Our approach to this problem as presented here is simply a method by which, with the use of an ordinary bone screw, the radius may be distracted the full distance from the ulna within the physiologic limits of the interosseous membrane which is still intact.

The first case treated in this manner consisted of putting a Roger Anderson half-pin unit into the radius by osteotomy near its proximal end, incorporating this half-pin unit in the plaster cast in such a manner that the radius was held a satisfactory distance away from the ulna during the healing period. This had the obvious disadvantage of a direct connection from the exterior to the bone with the possibility of infection, as well as the difficulty of anchoring it in plaster.

The next idea was to put a screw through the ulna in such a manner that it would impinge against the radius, and as this was screwed into the ulna it would distract the radius. In our cases as much as 2 cm. of space was thus achieved between these two bones and sufficient surrounding soft tissue could be obtained to adequately close over the osteotomy in the radius. No fascia lata was used and Gelfoam was placed in the depths of the wound covering the osteotomy in the end of the radius. These patients were treated by

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fixation with a plaster cast; the screw was removed between the third and fourth week to allow beginning motion of pronation and supination. This method, of course, has the disadvantage of necessitating the removal of the screw which passes through the ulna, but usually this can be done in the office under local anesthesia.

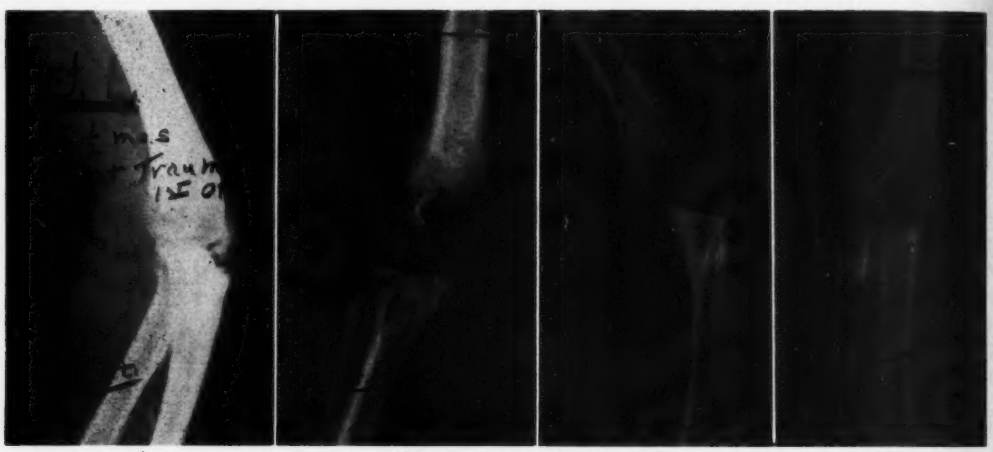
I would like to present 2 cases in which this method was used for the actual treatment of the pre-existing synostosis, and a third case of a Monteggia fracture, in which a synostosis could reasonably have been expected, and in which it is thought this was prevented by the prophylactic use of this distraction screw.

Report of Cases

Case 1. J. L. (No. 10240). This 24 year old jockey from Trinidad, British West Indies, fractured his right elbow in April, 1954, when, while holding his right arm outside of the automobile, his car was sideswiped by another, resulting in an open fracture of the elbow on this side (Fig. 1).

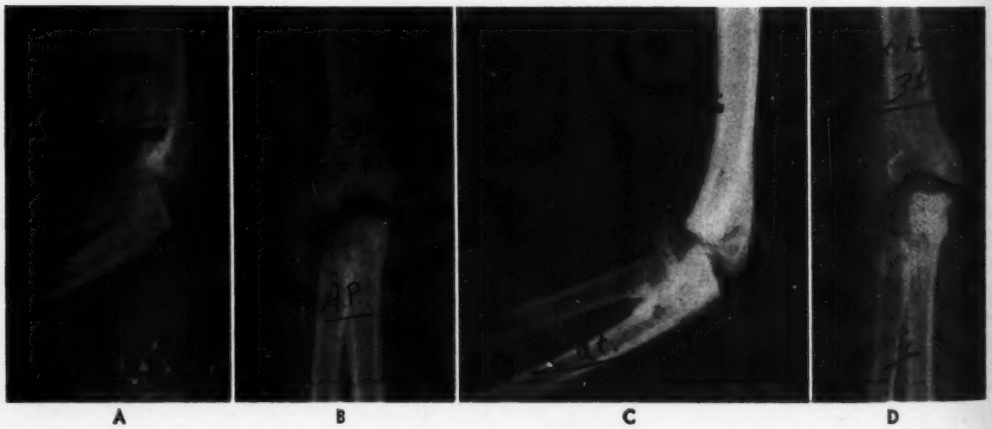
He was initially treated by open reduction in Trinidad, following which a complete radio-ulnar synostosis occurred (Fig. 2). An attempt at a second surgical

FIG. 1



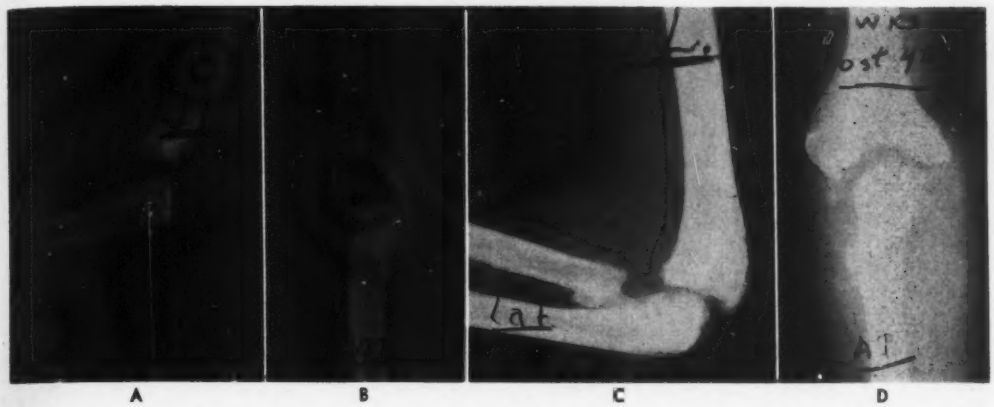
(Case 1) (A and B) AP and lateral views, two and one-half months after injury and following the first operation. (C and D) Three months after the second operation—note that synostosis has already occurred.

FIG. 2



(Case 1) (A and B) Views 6 weeks postoperative after removal of plaster following the third operation. (C and D) Fifteen weeks following the third operation; complete synostosis is again noted.

FIG. 3



(Case 1) (A and B) Five weeks following fourth operation; suggestion of ankylosis is now noted between the humerus and ulna; early bone is seen between the radius and ulna. (C and D) Ten weeks following fourth operation; synostosis has recurred; active motion is present in the elbow joint.

procedure prior to being seen by us met with a similar fate. We operated upon him with similar results (Fig. 3). Four months later, approximately one year from the date of his original injury, he submitted to a fourth procedure, this time using the distraction technic, using Steinmann pins which were incorporated in the plaster in an attempt to hold the radius away from the ulna (Fig. 4). Shortly after operation, it appeared that a recurrence of the synostosis was going to occur, but subsequent to this he began to show healing. Supination and pronation were resumed and later films demonstrated that no recurrence of the synostosis had occurred (Fig. 4,A).

The patient has returned to his former occupation of racing, at which he has again become proficient, but unfortunately we do not have an accurate measurement of his range of motion, although x-ray films mailed to us do not demonstrate a synostosis.

Case 2. H. E. C. (No. 14357). This 28 year old telephone operator was seen in the office on May 29, 1957. She had sustained a fracture of the left elbow region when she fell down a stairway on April 7, 1956, about 13 months before coming to the office. She had had 2 operations on the elbow, the first at about a month and the second one about 2 months after the injury. She also had had a manipulation of the elbow under general anesthesia and had received continuous physical therapy until she came to see us.

Examination revealed some swelling at the elbow area, an absence of supination and pronation, but flexion and extension from 80 degrees to about 145 degrees. She had definite crepitation with some pain and guarding when the elbow was flexed and extended; the grip was good. There was no sign of involvement of muscle or nerve. A diagnosis was made of synostosis between the proximal end of the left radius and ulna, with spur formation projecting into the antecubital space with limitation in flexion and extension (Fig. 5, A and B).

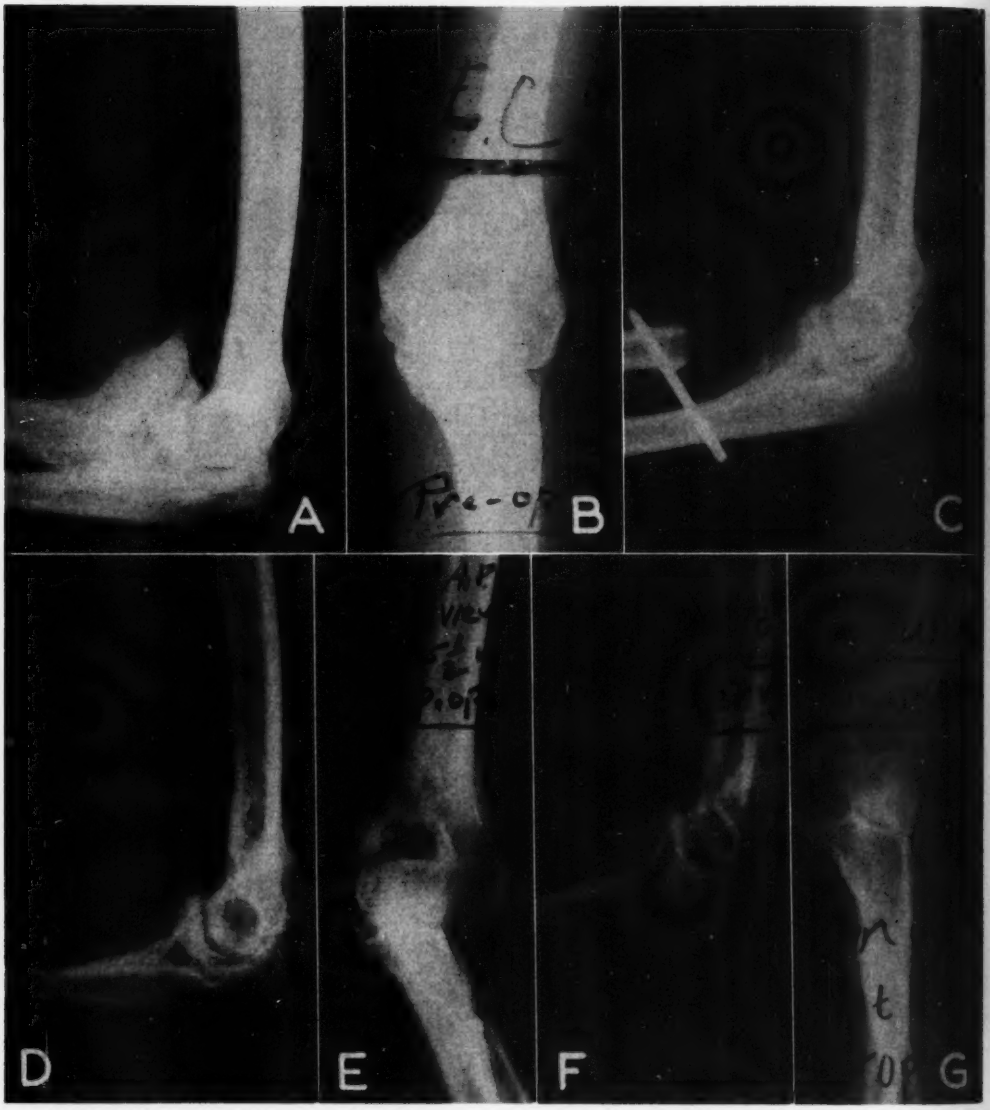
An operation was performed Sept. 27, 1957, 4 months after our first examination, and the synostosis and large bony spur mass were removed along with the proximal end of the radius. As shown in the x-ray film, the radius was held apart from the ulna by a threaded wire which was left in place for five and a half weeks along with a plaster cast immobilizing the elbow (Fig. 5, C). Gelfoam was put into the space between the radius and the ulna, but no fascia or other membrane.

The patient's last office visit here was on Nov. 10, 1958, about thirteen and a half months after her

FIG. 4

(Case 1) Final film showing no recurrence of synostosis although an abortive attempt was made.

FIG. 5



(Case 2) (A and B) AP and lateral views showing the complete synostosis and large bony spur before operation. (C) Film, five weeks after operation with distraction Steinmann pin in place (a simple bone screw is now used). (D and E) AP and lateral views, five and a half months following operation. (F and G) Nine months after operation and ulnar nerve transplant.

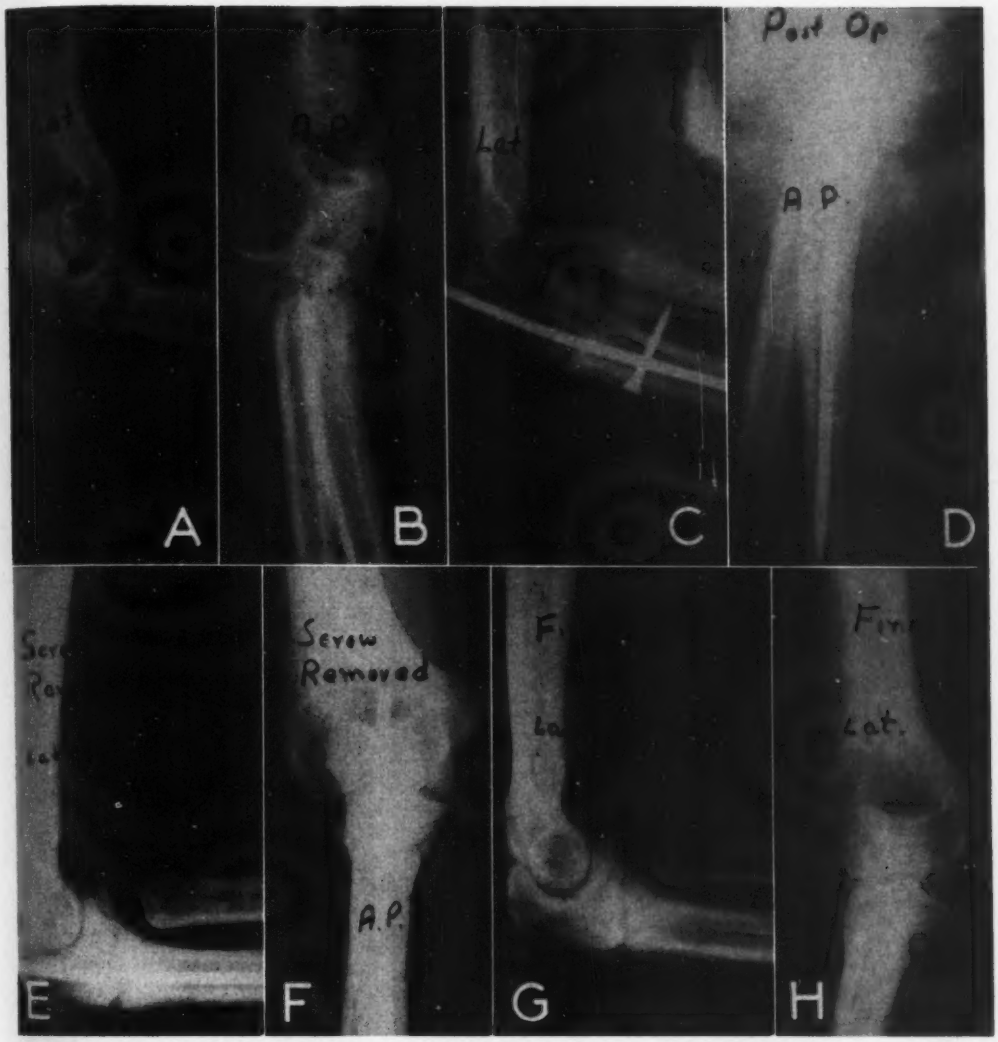
arthroplasty and she had then about normal flexion and extension to 150 degrees, and these motions were without pain or guarding. Pronation and supination were within normal limits and also without pain, guarding or crepitation (Fig. 5).

This patient has been back working as a telephone operator for several months and is doing her work very well without any disability.

Case 3. J. D. (No. 17650). This 48 year old colored male employee of a neighboring city's sanitation department injured his elbow when the packing mechanism of a garbage truck accidentally caught his arm, resulting in an open, crushing type injury to the left elbow and fractures of the proximal radius and ulna. He was treated by a local physician and 2 months later, because of continued pain and disability, was referred to our office by the insurance company for evaluation and recommendation (Fig. 6).

An arthroplasty was done, the ulna reduced and

FIG. 6



(Case 3) (A and B) AP and lateral views preoperatively, 2 months after injury, showing marked deformity and approximation of radius and ulna and potential synostosis. (C and D) AP and lateral views postoperatively after intramedullary pin has been inserted in the ulna, the radial head excised and distraction screw inserted. (E and F) Views showing removal of screw at 6 weeks. (G and H) Final result 6 months postoperatively; note that excellent union has concurred in the ulna and no evidence of synostosis is present.

fixed by internal fixation with a threaded Steinmann pin, and the radial head excised. Because of the severity of the condition, it was impossible to dissect out the various components of this malunion without exposing the radius and ulna to one another. Because of the fear of a possible radio-ulnar synostosis occurring, a single distraction screw was used to distract the radius from the ulna approximately three-quarters of an inch, the intervening area being held with as much surrounding soft tissue as could be obtained and the end of the radius covered with Gelfoam (Fig. 6). The distraction screw was removed 6 weeks postoperatively but the patient was left in plaster because of the slight bending which had occurred in the threaded pin in the ulna and the danger of nonunion loomed large in my mind at that time (Fig. 6). Three months postoperatively the patient was removed from plaster completely, and on the day his cast was removed he was able to flex to 60 degrees and extend to 100 degrees, although he had only slight pronation and supination. X-ray studies continued to show no evidence of a synostosis.

Five months postoperatively the threaded Steinmann pin was removed from the right ulna under general

anesthesia (Fig. 6). On his last evaluation 6 months after operation, the patient could flex to 60 degrees and extend to 145 degrees. He had 75% of both supination and pronation. He was discharged on that date with a 25% permanent partial disability of the right upper extremity.

Summary

We believe that the method outlined here presents a simple atraumatic technic of removing one of the major factors leading to a synostosis and should be useful both from the standpoint of prophylaxis and treatment.

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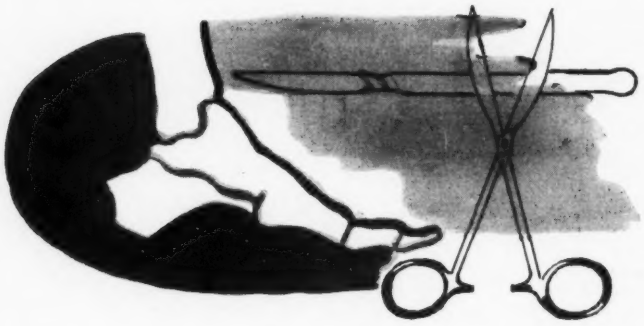
Discussion (Abstract)

Dr. Calvin Sandison, Atlanta, Ga. If all factors creating this condition of synostosis were known, the malady could be prevented. When we are able to control the cellular and chemical activity triggered by trauma, with resultant formation of bone, we not only can prevent synostosis but can apply the principle to better healing of bone. Control will come when we eventually understand the processes involved following tearing of periosteum and hemorrhage invading soft tissues. Experimentally, we arrive at various conclusions as to what happens in the bone cell, the fibroblast, and the surrounding fluids in trauma. Certainly we know, beginning with Ollier, that bone can form when the bone cell is activated with subsequent deposit of calcium salts. We also know with Leriche's idea, proved by others, that bone may form in soft tissues without the presence of a bone cell, and the chemist explains this on the hydrolysis of phosphorated esters combining with inorganic calcium locally to form the tricalcium phosphate of adult bone. Since no one has actually seen a fibroblast turn itself into a bone cell we must be skeptical of the third theory that such is a possibility, because we now know that a fibroblast never becomes an endothelial cell or *vice versa*. Clinically applied, as in Drs. Jewett and Brady's work on this problem, the mechanical factor of the separation of tissues with a minimum of hemorrhage would seem to add more control over the prevention of osseous formation. Just as distraction of a fracture is likely to produce nonunion, so may distraction of the radius from the ulna be quite important in holding in abeyance this inherent activity of the osteoblast and/or help to eliminate the laying down of bone salts in the repair of damaged connective tissue. Probably the sparsity of reports of the various surgical attempts to improve function in synostosis comes from discouraging results. It would seem that Drs. Jewett and Brady's procedure is worthy of note, in view of the improved function they have shown us, and particularly since the permanent use of metal or other materials foreign to soft tissues has been eliminated. I should like to try this procedure.



Total Esophagoplasty by Utilizing the Colon

ROBERT P. McBURNEY, M.D.,† *Memphis, Tenn.*

Numerous technics have had their day in the reconstruction of the esophagus. The colon has certain advantages of blood supply and mobility, and thus appears to be very usable. It has been used with increasing frequency as a substitute for the esophagus. Peristalsis is satisfactory.

NUMEROUS OPERATIONS have been devised and used in an effort to create a substitute for the esophagus. During the search for an improved procedure, surgeons have abandoned the makeshift methods of creation of skin tubes by plastic surgery, the antethoracic subcutaneous jejunal esophagus, and the connection of an esophageal fistula with a gastrostomy by rubber or plastic tubes. In recent years the stomach has been used most often as a substitute, with intrathoracic esophagogastrostomy being the preferred operation. The use of the jejunum either as a Roux-Y or as a long loop has also been popular, being used particularly by the Russian surgeon, Judin, and in more recent years by Petrov.[1] They have done this type procedure in more than 450 patients.

These procedures all have disadvantages. The use of jejunal loops is attended by a high incidence of ischemic necrosis, and when anastomosis is done high in the thorax, the postoperative mortality is excessive. The high mortality rate has restricted use of the jejunum to replacement for only a short segment of the lower esophagus, or it has necessitated its placement subcutaneously so that if necrosis results, death will not ensue.

The construction of skin tubes has been abandoned also because of the poor cosmetic effect, the numerous surgical procedures required to construct satisfactory tubes, and poor function of the created tubes.

The chief objection to esophagogastrostomy is the high incidence of esophagitis that follows. This has been as high as 50% in some reported studies.[2] Although the addition of drainage procedures at the pylorus may eventually lower the incidence of esophagitis, the recent studies of Kuykendall and associates,[3] at the Mayo Clinic, tend to show that drainage procedures of themselves do not prevent esophagitis in dogs. Because of these and other objections to past methods, during the last two years I have used the colon exclusively as a substitute for the esophagus.

Kelling[4] and Vulliet,[5] in 1911, working independently were apparently the first to utilize the colon as an esophageal substitute. Von Hacker,[6] in 1914, and Roith,[7] in 1923, reported cases in which the colon was used as a substitute.

Ochsner and Owens,[8] in 1934, reviewed the literature and found 20 cases of esophagoplasty in which the colon was used. In most of these the colon had been placed subcutaneously. Primarily due to the recognized value of antibiotic sterilization of the colon, the use of the colon has been more popular recently. In the past 5 years, over 100 cases have been reported in the literature and numerous others have been done but are unreported.

Esophagocologastrostomy lends itself well to cases of esophageal atresia when primary anastomosis cannot be done safely, for esophgeal stricture, esophageal carcinoma, esophageal varices, and for other conditions when esophageal resection is indicated.

Esophagoplasty may be accomplished by employing the right, the transverse or the left colon. In my first group of cases using this method, I used the right colon. However, recently I have used the left colon and have been more satisfied with the technical advantages as well as with the results.

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*Read before the Section on Surgery, Southern Medical Association, Fifty-Third Annual Meeting, Atlanta, Ga., November 16-19, 1959.

†From the Sanders Clinic, and the Department of Surgery, the University of Tennessee College of Medicine, Memphis, Tenn.

The colon may be brought into the upper thorax or into the neck through the esophageal hiatus, through a separate incision in the diaphragm, or by way of a substernal tunnel in the anterior mediastinum.

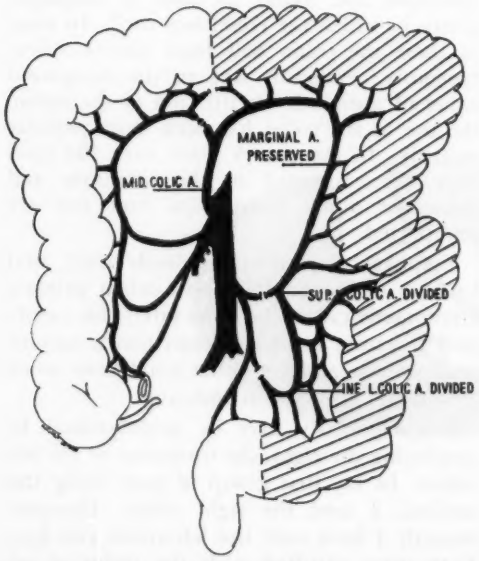
Advantages of the use of the colon are as follow:

(1) The blood supply of the colon usually allows one to mobilize a sufficient length to reach the pharynx and at the same time have adequate circulation to the distal end.

(2) The colon is relatively resistant to acid-peptic digestion. Ivy,[9] Wangensteen[10] and others have shown that the colonic mucosa is more resistant to acid-peptic digestion than the esophagus or small bowel. In over 100 cases reported in the literature, or of which I have knowledge, only 3 patients were found to have acid-peptic colitis.

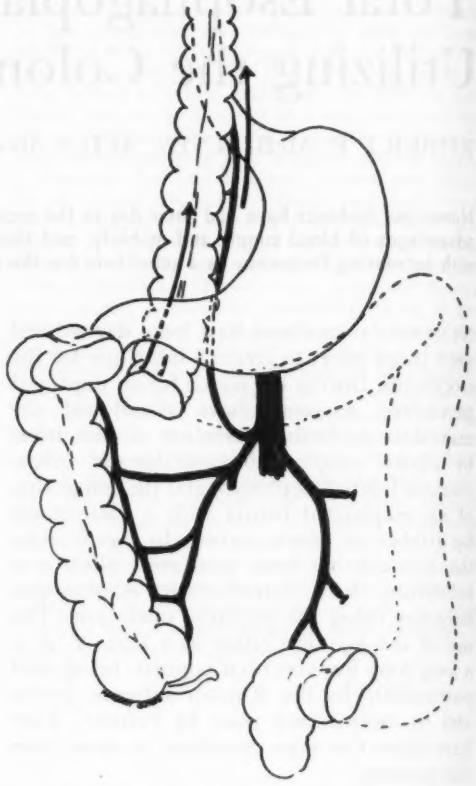
(3) Another advantage of the use of the colon over esophagogastrostomy is that the stomach remains in its normal location performing its normal function as a reservoir and does not function primarily as a transit tube. Consequently, the patient with esophagocologastrostomy has fewer digestive disturbances and better nutrition than the patient with esophagogastrostomy.

FIG. 1



The left colon is mobilized from mid-transverse area to the sigmoid. The middle colic and marginal arteries are preserved.

FIG. 2



The mobilized segment of colon is brought into the upper abdomen behind the pylorus.

(4) By using the colon as a total esophageal substitute, a proximal anastomosis can be done in the neck. If leakage occurs, only a small focal abscess and/or fistula results. If anastomosis is done in the pleural cavity and leakage occurs, empyema and severe sepsis can develop, often ending with death of the patient.

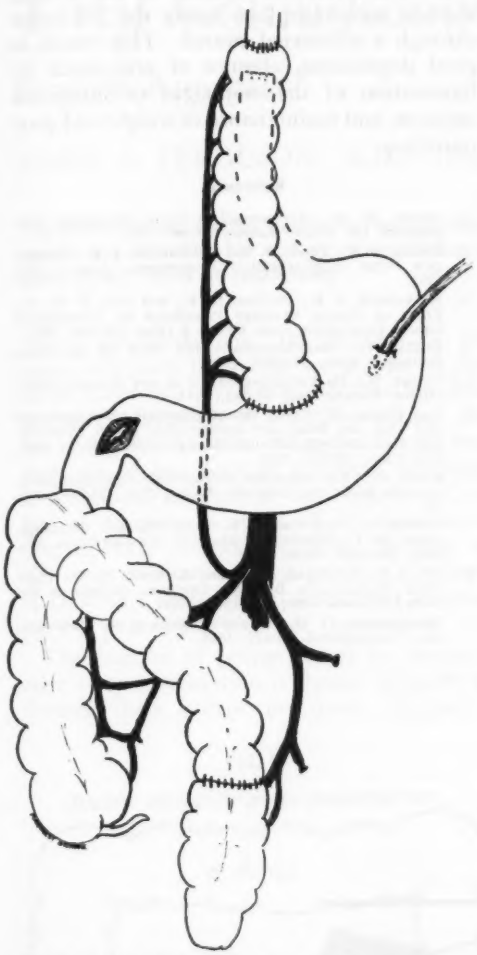
(5) One can do a total esophagectomy for carcinoma of the esophagus if total esophagocoloplasty is done. This should increase the percentage of 5 year survivals.

Technic

The patient is admitted to the hospital a few days before surgery, and the colon is sterilized by neomycin and sulfathalidine. Any necessary measures to improve nutrition and blood volume are also taken at that time.

At operation the patient is placed in the

FIG. 3



The colon is brought into the neck in a substernal position. Anastomosis is made to esophagus and stomach. Colocolostomy, pyloroplasty and gastrostomy are also performed.

supine position, and a long midline incision is made. The left marginal vessel is identified, and if well developed on the left side this portion of the colon is mobilized. The left colic, and if necessary for length, the first sigmoid vessel, are ligated at their origins, being careful to preserve the marginal vessels intact. The colon is then divided at the sigmoid area and in the mid-transverse area, the blood supply coming entirely from the middle colic artery and vein (Fig. 1). The transverse colon is anastomosed to the sigmoid. The free segment of colon is then brought into the upper abdomen behind the stomach and the proximal portion of colon (the transverse colon) is anatomosed to the upper stomach, end to side (Figs. 2 and 3). When this anastomosis is begun, a second surgical team begins its work in the neck making an incision along the anterior border of the sternomastoid muscle. The cervical esophagus is mobilized and divided, and the distal portion is closed with two rows of interrupted sutures.

A substernal tunnel is then developed by the abdominal team and the cervical team. Both teams are careful not to enter the pleural space on either side.

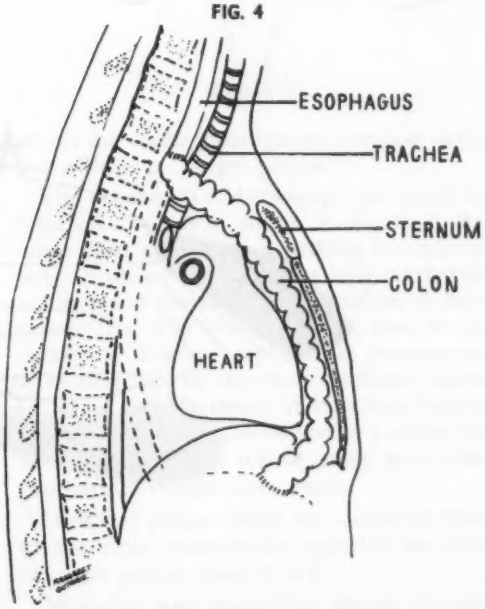
The colon is passed from the abdomen through the substernal tunnel, and anastomosis is done in the neck, end-to-end, using two rows of interrupted sutures (Fig. 4). The operation is then completed by pyloroplasty in the cases of carcinoma of the esophagus and a tube gastrostomy of the Stamm type (Fig. 3).

In cases of carcinoma of the esophagus, a total esophagectomy is done as a first stage procedure, and following recovery from this a new esophagus is constructed.

Results

This procedure has been done by myself

FIG. 4



Sagittal view illustrating the position of the colon segment in the substernal position.

and associates in 8 cases with one death. My colleagues, of the Thoracic Surgical Department, at the University of Tennessee College of Medicine, have used this procedure in approximately 20 additional cases with about a 10 to 15% mortality.

The results with reference to swallowing have been exceedingly good. Apparently it makes little difference whether the colon segment is placed antiperistaltic or isoperistaltic. In one case where the esophagus presented stricture from pharynx to stomach, it was necessary to dilate the area of esophagocolic anastomosis. This produced excellent swallowing function.

In two cases, an esophagocolocutaneous fistula complicated the postoperative course. In one of these closure was rapid and the result was good. In the other case the fistula continued to drain until the patient's death from carcinoma.

Summary

1. Interposition of a segment of colon has been, in my experience, the most satisfactory method of esophagoplasty.

2. The preferred method of use is total thoracic esophagoplasty using the left colon through a substernal tunnel. This results in good deglutition, absence of acid-peptic inflammation of the esophagus or interposed segment, and maintenance of weight and good nutrition.

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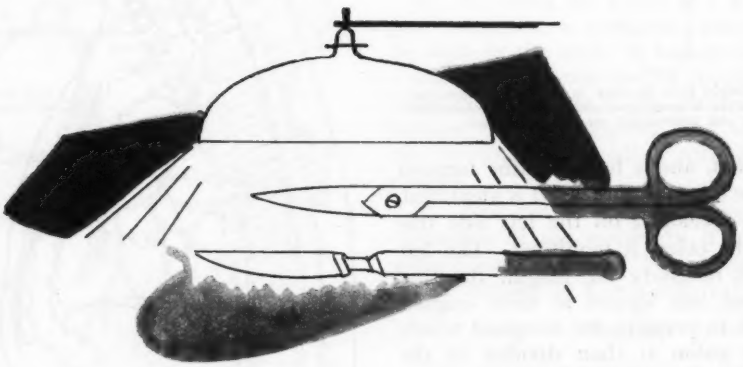

Total Colonoscopy: A Systematic Surgical Approach*

JAMES A. FERGUSON, M.D.,† *Grand Rapids, Mich.*

The author points up the number of polyps which may be missed upon examination by barium enema. He describes his technic of examining all segments of the colon under direct vision at laparotomy.

SIMPLE COLOTOMY and polypectomy is no longer adequate treatment for polyps of the colon diagnosed by x-ray examination following the injection of a barium enema. In the spring of this year Waggener,[1] who was then one of our surgical residents, reported to a regional meeting of the American College of Surgeons a study of 50 consecutive cases of total colonoscopy. Our findings in this series substantiate the previous findings of Deddish,[2] Bacon[3] and others and emphasize the procedure's extreme importance.

The number of polyps found by preoperative x-ray examination is shown in figure 1. Because these polyps previously diagnosed

FIG. 1

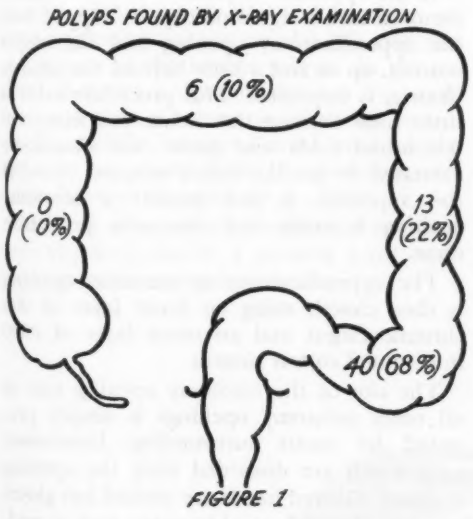

FIGURE 1

FIG. 2

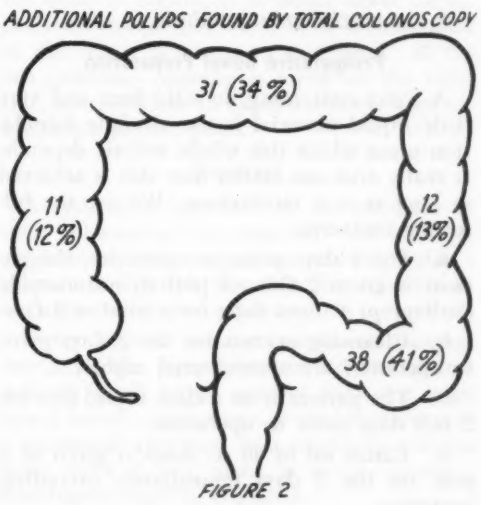

FIGURE 2

set off the whole investigation, we have designated them as "target polyps."

The number of additional polyps found by total colonoscopy is shown in figure 2. Because these polyps are something in addition to the principal ones we have designated them as "dividend polyps." By comparison of these two figures, it is quite apparent that the accuracy of diagnosis by barium enema and x-ray decreases in the more proximal colon. In all of these patients, at least two barium enemas were done, the second to confirm the first and, in a very few of them, more than two barium enemas were done.

Dividend polyps, those not suspected prior to operation, numerically exceeded the total of target polyps almost 2 to 1.

Mortality and morbidity should be considered. There were no deaths; the morbidity

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was minimal in this particular group of 50 patients.

In the light of the foregoing considerations, it is clearly apparent that only total colonoscopy is adequate treatment for polyps of the colon and that the mortality and morbidity are not prohibitive.

As our experience with these patients advanced, a systematic approach to the entire problem from the viewpoint of surgical technic evolved.

The following headings will be considered:

1. Preoperative preparation of the bowel.
2. Type of incision.
3. Intra-abdominal technic.

Preoperative Bowel Preparation

A colon containing no solid feces and very little liquid material is the absolute foundation upon which this whole technic depends. It really does not matter how this is achieved as long as it is satisfactory. We use the following measures:

a. For 4 days prior to operation, the patient is given 2 Gm. of phthalylsulfonamide (Sulfaprep) 4 times daily for a total of 8 Gm.

b. Cleansing enemas for the 3 days prior to operation are administered nightly.

c. The patient is on a clear liquid diet for 2 full days prior to operation.

d. Castor oil in 60 cc. doses is given at 2 p.m. on the 2 days immediately preceding operation.

e. Cleansing enemas are given 2 hours prior to operation.

Using these measures we have been able to produce very consistent, excellent conditions under which to perform total colonoscopy. There are other ways of producing the same results, but we know that we can expect with confidence a colon which contains no solid feces, with perhaps a small amount of brownish, liquid material which does not obstruct visualization and may be easily removed by aspiration. In many cases there is literally nothing in the colon and suction is not necessary.

Incision

An inadequate or poorly placed incision makes the procedure much more difficult than it should be and we use a long, left, paramedian incision worthy of the scope of the operation. It is the same incision which we would use for total colectomy. A flank to flank, transverse incision near the umbilical level, gives exposure which is comparable, but sometimes even then it is difficult to gain ready access to the rectosigmoid or to a high splenic flexure.

Intra-abdominal Technic

As soon as the incision is made and the peritoneum opened, an abdominal wall retractor is inserted in the right side of the wound and the ileocecal junction is identified with no palpation or manipulation of any of the other abdominal organs. A rubber-shod clamp is placed at the ileocecal junction and then, and only then, are the intra-abdominal organs inspected and palpated in the usual manner. This precaution prevents the milking-out of small bowel content into the colon and in and of itself has greatly enhanced the ease and accuracy of subsequent inspection of the entire colonic mucosa.

Contrary to other recommended approaches, the colon is visualized in a clockwise fashion starting first at the cecum which is usually the well side of the colon. I say the well side because most polyps diagnosed preoperatively occur in the descending and sigmoid portions of the colon.

If the appendix is present, it is invariably removed and a sigmoidoscope is slipped into the appendicotomy opening and the entire mucosa, up to and a little beyond the hepatic flexure, is inspected. This procedure takes a little time because the cecum has many intraluminal folds and great care should be exercised to see the entire mucosal area. If the appendix is not present a cecotomy opening is made and the same procedure done.

The appendicotomy or cecotomy opening is then closed, using an inner layer of 000 chromic catgut and an outer layer of 0000 interrupted cotton sutures.

The site of the cecotomy opening and of all other colotomy openings is simply protected by moist surrounding laparotomy pads which are discarded after the opening is closed. Gloved hands are washed but gloves are not changed at this point and a mid-transverse colotomy is made. This again is protected by surrounding moist laparotomy pads and the sigmoidoscope is inserted to in-

spect the right half of the transverse colon and the hepatic flexure. The scope is withdrawn to the point of the colotomy and inserted in the left transverse colon to the splenic flexure. This transverse colotomy opening is closed in the same manner as described, the laparotomy pads discarded and the gloved hands washed. A sigmoid colotomy is then made, protected in the same manner, and the scope introduced upward into the descending colon to the splenic flexure. The scope is drawn back to the point of colotomy and then inserted distally down through the sigmoid, well into the upper rectum. The instrument should always reach into that part of the rectosigmoid or upper rectum which is in the hollow of the sacrum and which is certain to have been inspected preoperatively by proctosigmoidoscopy.

Measures should be taken to insure absolute visualization of the entire mucosa of the colon. The sigmoid or the descending colon should always be mobilized, if necessary, to provide ready access to the splenic flexure.

The number of colotomy openings must be an individual matter, and there should be as many as is necessary to accomplish the mission. In 16 of the patients in our series total colonoscopy was done through two colotomy openings. These people represent the first of the series in whom we were not starting with the well side and in whom we were beginning usually on the left side and in the area of the known polyps. In the patients in whom a sigmoid colotomy was made first, and then a transverse colotomy, an unusually mobile hepatic flexure enabled the scope to be passed from the mid-transverse colon down to the cecal tip.

In 30 of our patients 3 colotomy openings were required, and in 4 patients 4 colotomy openings were necessary.

We have experimented with several methods of intraluminal marking of the extent of visualization in any one of the limbs of the colon with the hope that we would be certain to overlap the same area from the opposite direction and thus be positive that the entire colonic mucosa had been inspected.

We have tried clips, the submucosal injection of dye, electrocoagulation, etc., for this purpose, but now believe it is unnecessary if enough colotomies are made to insure easy overlapping of the fields of inspection.

When the last colotomy opening is made in the sigmoid region, it is much easier to express air which may have been accumulated in the colon proximal to this point. If the last colotomy opening is made on the right side, it is difficult to express accumulated air backward to that point.

Summary

A systematic approach to the problem of total colonoscopy is presented, and it is reemphasized that meticulous and dependable preparation of the bowel is the foundation for a successful procedure.

Other keys to success include an incision worthy of the procedure, precautions against milking small bowel content into the large bowel before colonoscopy is undertaken, and a systematic approach in a clock-wise fashion from right to left using as many colotomy openings as may be required.

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Know Your Southern Medical Association

The Scientific Assembly

The scientific work of the Southern Medical Association is divided into twenty Sections, running the gamut from Allergy to Urology. Section work is augmented by general sessions, joint sessions and symposia on timely subjects such as Nuclear Medicine, Medical Economics (the business side of your practice), Geriatrics and Cerebrovascular Disease,—all designed for one purpose—to help the doctor practice better medicine.

Background

The modern concept of section work was instituted by the Association at its *first* annual meeting in Birmingham in 1907 when scientific programs were presented in three Sections: Medicine, Surgery and Ophthalmology. Thus the basic reason for the founding of the Association in 1906—"to provide a greater opportunity for self-improvement and achievement"—was fulfilled at the postgraduate level from the beginning.

Growth of Sections

As specialization developed, the need for a forum for the discussion of problems and progress in these new fields developed also. The Southern Medical Association has been quick to sense these needs related to special interests, and has created sections for their benefit. Often, the Southern Medical Association has led the way in recognition of specialties by creating sections where the finest work in the South in these fields could be presented.

The Scientific Assembly Today

The Sections presently composing the Scientific Assembly of the Association and the dates of their establishment in chronological order are as follow:

Medicine	1906
Surgery	1906
Ophthalmology and Otolaryngology	1906
Public Health	1912
Industrial Medicine and Surgery	1913
Pediatrics	1917
Gastroenterology	1917
Urology	1919
Obstetrics	1920
Orthopedic and Traumatic Surgery	1920
Radiology	1920
Neurology and Psychiatry	1921
Dermatology and Syphilology	1922
Pathology	1923
Gynecology	1928
Allergy	1933
Proctology	1937
Anesthesiology	1937
General Practice	1941
Physical Medicine and Rehabilitation	1942

One Section Discontinued

The Section on Medical Education and Hospital Training was created in 1916 and discontinued in 1954. Why? Simply because other organizations were formed in the interim, many national in scope, which meet more fully the forum needs of those engaged in medical education with its complex facets of administration, finance and personnel, many of which are related not at all to the needs of the practicing physician.

During the life of this Section, the Association made an outstanding contribution to medical education and hospital training in the South. The names of most leading deans and teachers in the territory were closely identified with the work of this Section in a period when the *quality* of medical education varied greatly from school to school. No general medical association or society *per se* can claim more credit for elevating the standards of medical education and intern and residency training in the South during this period.

How New Sections Come About

The basic test for forming a new section is whether or not the specialized needs of a substantial number of physicians require a forum of *more* than one session. Thus "trial runs" on the appeal and value of a given subject or field of interest are made in the form of general sessions and symposia. These special subjects include geriatrics, medical economics,

cerebrovascular disease, nuclear medicine and other timely topics.

When interest in, and the need for more than a single session is demonstrated, and the specific needs cannot be incorporated into presently existing Section programs, a new Section is created for that special need.

How Section Work Is Prepared

The program of all the Sections is prepared *by physicians for physicians*. Each Section elects its own officers—a Chairman, Vice-Chairman, and a Secretary, with primary responsibility for program-planning resting on the Secretary.

At least *nine* months before an annual meeting, the Secretaries of the Sections meet with the *Committee on Scientific Work* to plan the program. This five-man Committee works in close cooperation with the Secretaries to see that well-rounded programs are planned for each Section. The Committee also arranges general sessions, joint sessions and symposia.

Scientific and Technical Exhibits

Adding greatly to the teaching value of an annual meeting, the Association presents both technical and scientific exhibits, each numbering in the hundreds. Highest standards for both types of exhibits are maintained by Committees which review all proposed exhibits on the bases of quality, originality, and *teaching value*. These exhibits, carefully screened, give the busy physician a look at not only "What's New in Medicine," but what's solid as a result of research and experimentation.

Freedom of Choice

A physician attending a Southern Medical Association meeting is not required to attend only *one* Section. He can pick and choose to his heart's content—and its capacity! There need not be any gaps or lay-overs in his three and one-half days of attendance. Thus the General Practitioner, for example, may attend the Sections on Obstetrics, Gynecology, Dermatology, Surgery, or what not. He may spend *his* time where, in *his* opinion, it will be most profitable to *him*.

And the physician need not have to guess or "go see" what a given Section has to offer him. Preliminary programs (usually complete) are mailed to more than 40,000 physicians at least *two months* in advance of the meeting. Thus the physician can *plan* his scientific itinerary *in advance* in order to receive maximum value for the time he spends in scientific sessions.

This freedom to "pick and choose" provides great program flexibility, variety and personal appeal. At the same time this plan enables the Southern Medical Association to reach one of its continuing goals—helping doctors practice better medicine.

V. O. F.

SOUTHERN MEDICAL NEWS

The Section of Ophthalmology and Otolaryngology of the Southern Medical Association announces that they are now accepting papers by physicians of either specialty living in the area of the Southern Medical Association for consideration for presentation at the next annual meeting to be held in St. Louis, Missouri, October 31-November 3, 1960. The paper or an abstract of the paper may be sent to the Secretary, Dr. Albert C. Esposito, Suite 1212, First Huntington National Bank Building, Huntington, West Virginia, as soon as possible.

ALABAMA

Dr. Winston A. Edwards, Wetumpka, is President of the Alabama Academy of General Practice.

Dr. Francis A. Marzoni, Birmingham, is Vice-President of the Southeastern Society of Plastic and Reconstructive Surgeons.

Dr. H. N. Carmichael, Fairfield, is President of the Birmingham Academy of Medicine. Other officers include Dr. Dewey A. White, Vice-President, and Dr. Perry A. Morgan, Secretary-Treasurer, both of Birmingham.

Officers of the Birmingham Clinical Club are Dr. Paul Woodall, President; Dr. Albert Casey, Vice-President; and Dr. Joseph Sewell, Secretary-Treasurer.

Drs. James K. Ward and Hardin Ritchey, both of Birmingham, are President and Secretary-Treasurer, respectively, of the Alabama Academy of Neurology and Psychiatry.

Continued on page 525

EDITORIALS

GLOMERULAR AND RETINAL LESIONS IN DIABETES MELLITUS

Capillary aneurisms in the retina of diabetic patients have been recognized since their first description by Ballantyne[1] in 1944. Hyalinization of segments of the glomerular loops, the condition first described by Kimmelstiel and Wilson[2] in 1936, has been called *intercapillary glomerulosclerosis,* or the Kimmelstiel-Wilson Syndrome when associated with albuminuria, hypertension, the nephrotic retention of water and frequently diabetic retinitis. The temptation to call the Kimmelstiel-Wilson glomerular lesion an aneurism like the retinal lesion was difficult to resist. An observation seized upon by a number of workers and exploited past its original context was that of Rich[3] (1950) who described aneurismal dilatations of the glomerular loops, resembling Kimmelstiel-Wilson's intercapillary glomerulosclerosis, in rabbits made diabetic with cortisone. The fat was in the fire. The renal lesion of Kimmelstiel-Wilson in the human was an aneurism of the glomerular loop, and probably it was produced by cortisone.

The final quietus to such specious speculations has just been furnished by electron microscope studies of diabetic glomerulosclerosis by Farquhar, Hopper and Moon[4] (1959). The basement membrane of the glomerulus in diabetic glomerulosclerosis is thickened, not thinned as in an aneurism, and the lesion is the deposit in the glomerulus of a hyaline material initially in relation to the endothelial cells. Kurtz and McManus[5] (1959) relate the central endothelial-type cells of the human glomerulus to interluminal cell aggregates, these being initially affected in the intercapillary glomerulosclerosis of Kimmelstiel and Wilson.

The electron microscope seems to have established the nonaneurismal nature of the glomerular lesions in diabetes mellitus. Further explanation of the lesion of Rich has been found in the cases of Johnson (to be published) which have been described and illustrated by McManus[6] (1957 Seminar). These are true aneurisms of the glomerular loops occurring in patients on extended cortisone therapy. They are comparable to the animal lesions produced by Rich (1950), by Bloodworth[7] (1955) and by others and are quite different, in thin sections and with stains for basement membrane, from the diabetic lesions.

Tracing back the confusion about the glomerular lesion in diabetic glomerulosclerosis as resembling the capillary aneurism of diabetic retinitis, we can find only two common features—both occur in diabetes mellitus and both are round in microscopic section. If there is a lesson to be learned from the story of the diabetic lesions it is, "All things round in capillaries are not aneurisms," perhaps an equivalent to the, "All is not gold that glistens."

J. F. A. McMANUS, M.D.

1. Ballantyne, A. J., and Loewenstein, A.: Retinal Microaneurysms and Punctate Haemorrhages, Brit. J. Ophth. 28:593, 1944.
2. Kimmelstiel, P., and Wilson, C.: Intercapillary Lesions in Glomeruli of Kidney, Am. J. Path. 12:83, 1936.
3. Rich, A. R., Berthrong, M., and Bennett, I. L., Jr.: Effect of Cortisone upon Experimental Cardiovascular and Renal Lesions Produced by Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. 87:549, 1950.
4. Farquhar, M. G., Hopper, J. H., Jr., and Moon, H. D.: Diabetic Glomerulosclerosis: Electron and Light Microscopic Studies, Am. J. Path. 35:721, 1959.
5. Kurtz, S. M., McManus, J. F. A.: A Reconsideration of the Development, Structure, and Disease of the Human Renal Glomerulus, Am. Heart J. 58:357, 1959.
6. McManus, J. F., Dieckmann, W. J., McCartney, C. P.: Kidney Pathology in Toxemia of Pregnancy, Seminar Report 2:13, Spring, 1957.
7. Bloodworth, J. M. B., Jr., and Hamwi, G. J.: Histopathology of Experimental Glomerular Lesions Simulating Human Diabetic Glomerulosclerosis, Am. J. Path. 31:167, 1955.

SYMPOSIUM ON NUCLEAR MEDICINE

In this issue appear the papers given at a Symposium devoted to the use of radioactive isotopes in the field of medicine,—investigative, diagnostic and therapeutic. This marks the progress of biophysics as an ever-expanding field of medicine.

Chemistry, in one way or another, has been associated with medical knowledge for centuries,—first because of natural substances used in treatment. The middle of the nineteenth century saw the birth of biochemistry which gathered momentum during the succeeding century and, if not gathering more, has at least showed no signs of slowing.

Physics came into the study of biologic and

physiologic processes as the galvanic current in the study of nerve stimulation, published by Pflüger a hundred years ago. However, twenty years before the galvanic current had been used in the treatment of a urethral stricture, and galvanocautery had had an expanding use in subsequent decades. Helmholtz applied optics to medicine with the ophthalmoscope in 1851. These were high points in the application of physical phenomena to medicine.

In looking at atomic medicine, one should recall that the Russian chemist, Mendeléeff, discovered the periodic law and recorded it in 1869. Roentgen observed the "x-ray" in October, 1895. But the phenomenon of radioactivity was not recognized until 1896, when Becquerel found it in uranium. The Curies isolated radium from pitchblende in 1898. Quickly the x-ray was applied to diagnosis with an ever-expanding use from 1896 when it was first used to find a bullet in a leg. The effect of the x-ray upon tissue, and especially carcinoma was recognized by 1899. Deep x-ray therapy was introduced in 1903. It was used also in the treatment of leukemia that year. Abbe, an American surgeon published, in 1914, studies demonstrating that the beta rays of radium were effective in destroying cells. By 1916 it was shown in this country that radium could be an occupational hazard.

The x-ray continued, through refinement of technics, to be of immeasurable value in diagnosis. With higher and higher voltage it, along with radium, offered a therapeutic weapon in malignancy and in certain benign diseases.

The modern era of atomic energy began in 1930 when E. O. Lawrence, physicist at the University of California, invented the cyclotron and "smashed" the atom. Thereby the transmutation of elements, the lodestar of the alchemist of the Middle Ages, became a reality. New elements were discovered, and nonradioactive elements could be made radioactive. These, the radioactive isotopes, immediately took their place in medicine. Radioactive tracer compounds were used in the 1930's to study the metabolism of amino acids and fats. The use of radioactive phosphorus in the treatment of leukemia and polycythemia vera was recorded in about 1939. Radioactive iodine after several years use in the study of thyroid function was used in treatment first in 1942.

Then came the events which led from the Uranium Committee, formed in 1940, through the first successful nuclear chain reaction, to the atomic bomb and Hiroshima. After this the Oak Ridge National Laboratory was converted, after the war, to the peacetime production of isotopes for medical and other scientific uses.

And this historical background brings us to the papers of the Symposium which appear in this issue—the description of the use of radioactive isotopes in diagnosis and treatment. One additional facet of the story deserves some emphasis, namely the use of tagged substances and chemicals in basic studies aimed at the understanding of biologic processes in fundamental research. From such studies will come some of the knowledge which the physician will use in a decade hence in diagnosis and in the treatment of his patients.

INSTRUCTIONS TO CONTRIBUTORS

Exclusive Publication: Articles offered for publication must be contributed solely to the Southern Medical Journal.

Manuscripts: Manuscripts should be original copy, typewritten, double-spaced, with wide margins. Because of lack of space, it is necessary to limit the number of bibliographic references to twenty. Footnotes and references should conform to the following style:

1. Doe, J. E.: What You Should Know about It, South. M. J. 50:711, 1950.

Illustrations: Black and white glossy prints, preferably 5 by 7 inches, and drawings in India ink on white paper are required. The author's name, number and indication of top, if doubtful, should be attached. Necessary plates not exceeding six, or one and a half pages, will be furnished by the Journal.

Reprints: Reprints are available at publisher's cost. An order form will accompany author's galley proof and should be returned with the galley to the Editor.

Book Reviews: Books and monographs submitted for review should be mailed to the Editor. Acknowledgment will appear in the Journal. Selection rights reserved.

Editorial Address: All manuscripts, corrected galley proof, reprint orders, books for review and related correspondence should be addressed to the Editor, R. H. Kampmeier, M.D., Vanderbilt University School of Medicine, Nashville 5, Tennessee.

Business Address: All correspondence related to membership, subscriptions, advertising, and other business should be addressed to the Southern Medical Association, 2601 Highland Avenue, Birmingham 5, Alabama.

25 YEARS AGO

Sternal Puncture in Clinical Hematology.*

"Recent advances in our knowledge of the disorders of the blood have made clinicians increasingly conscious of the necessity for accurate hematologic diagnosis. Formerly a routine physical examination and blood count by an intern or the hospital laboratory was considered adequate in studying cases of anemia. Today in our larger hospitals the hematologist is called in consultation . . . and it is important that he have at his command every possible diagnostic facility.

"During the past year the author has employed sternal puncture routinely on all cases of blood dyscrasias seen in consultation. Needless to say the results have been extremely interesting.

"The technique of sternal puncture has been described in detail elsewhere (in press at the time), so that a brief resumé only will be given. A small area on the skin overlying the sternum opposite the 3rd interspace is painted with iodin, and novocain is injected into the skin, underlying tissues and periosteum. A specially constructed needle is then driven into the spongy bone and 10 cc. of a bloody fluid aspirated and mixed with 2 cc. of a 1.4% sodium oxalate solution. This mixture is centrifuged and smears are made of the buffy coat and stained with Jenner-Giemsa stain. A differential count of 1000 cells is then made.

"This method is practically painless and is well adapted to ward and clinic use. The small puncture heals up readily and the procedure can be repeated at frequent intervals.

"The marrow picture not only makes the diagnosis more definite, but presents a broadening insight into the changes going on in the formative tissues. A few selected cases will aid in illustrating the value of this technique. . . .

"Summary. From a study of the cases cited, it is seen how valuable sternal puncture may be in differentiating the various types of anemia, in establishing the diagnosis of leukemia in doubtful cases and in differentiating aleukemic lymphatic lukemia from agranulocytosis. In 1 instance it was even possible to see tumor cells in the sternal marrow, although this is very unusual.

"This method of investigation does much more for the hematologist, however, than aid him in his diagnosis. It gives him an insight into the fundamental processes underlying his findings in the peripheral blood and opens new avenues of clinical research. It is now possible to study the changes in the bone marrow almost as frequently as those in the peripheral blood and to observe the direct effect of therapy on the formative tissue."

The Editor's footnote read, "While the method of sternal puncture is undoubtedly of great value in the study of anemia, the examination of the material obtained in tissue sections rather than in smears would seem to be preferable. Imprint preparations break up fewer cells than do smears; with smears, preliminary suspension in serum has advantages.—Editor."

*Reich, Carl: A Study of the Diagnostic Value of Sternal Puncture in Clinical Hematology, Am. J. Med. Sc. 189:515, 1935.

BOOKS RECEIVED

Autogenous Vein Grafts. By W. Andrew Dale, M.D., Assistant Professor of Clinical Surgery, Vanderbilt University School of Medicine, Nashville, Tenn. 117 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1959. Price $6.00.

Diseases of the Nervous System in Infancy, Childhood and Adolescence. By Frank R. Ford, M.D., The Johns Hopkins Hospital, Baltimore. Fourth edition. 1,326 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1960.

Elongation Treatment of Low Back Pain. By George H. Hassard, M.D., Department of Physical Medicine and Rehabilitation, Veterans Administration and University of Oklahoma Hospitals; and Charles L. Redd, B.S., Physical Therapist, Alton, Ill. 76 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1960. Price $4.50.

Intussusception in Infants and Children. By Mark M. Ravitch, M.D., Associate Professor of Surgery, The Johns Hopkins University School of Medicine. 119 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1959. Price $9.00.

Alcoholism. Proceedings of First Annual Conference of Community Mental Health, Washington University. Edited by David J. Pittman, Ph.D., Research Assistant-Professor, Departments of Psychiatry and Sociology, Washington University. 96 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1959. Price $3.75.

Electrohysterography. By Saul David Larks, Ph.D., Assistant Professor of Biophysics, University of California School of Medicine. American Lecture Series. 120 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1960. Price $5.75.

Surgical Philosophy in Mass Casualty Management. By Warner F. Bowers, M.D., Col., M.C., Chief, Department of Surgery, Tripler U.S. Army Hospital, Honolulu; and Carl W. Hughes, M.D., Lt. Col., M.C., Assistant Chief, Department of Surgery, Tripler U.S. Army Hospital. 197 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1960. Price $6.75.

ERRATA

In the March issue, page 379, editorial entitled "The General Practitioner and Psychiatry," the second paragraph should read "The American Academy of General Practice" instead of "The Association for the Advancement of General Practice."

APPLICATION FOR HOTEL ACCOMMODATIONS

Southern Medical Association

Saint Louis, Missouri

October 31-November 3, 1960

IMPORTANT: The Convention Reservation Bureau will make hotel assignments upon receipt of this official housing application provided that the application is properly filled out and all necessary information is given. In order that a fair distribution of accommodations can be made to the greatest number of members, all rooms will be assigned on a strictly "first come, first served" basis.

INSTRUCTIONS: *(A) Single rooms are limited in number. Please arrange to occupy double bedded or twin bedrooms if possible. No block reservations will be made.*

(B) Be sure to indicate your arrival time in St. Louis. Reservations will be held only until 6:00 p.m. of the day you indicate when you will arrive in St. Louis. Failure to notify the hotel of any last minute change in your arrival time may result in the cancellation of your reservation.

(C) Write the Convention Reservation Bureau, 911 Locust Street, St. Louis, if you wish to cancel the reservation or make any change in your reservation and NOT the hotel to which you were assigned. This will enable them to reassign rooms that have been cancelled.

(D) If the hotels of your choice are unable to accept your reservation, the Convention Reservation Bureau will make as good a reservation as possible elsewhere provided that all hotel rooms available have not already been taken.

Hotel	For one person	For two persons Double Bed	For two persons Twin Beds	2-Room Suite Parlor & 1 Bedroom
CLARIDGE	$5.50-$ 8.00	$ 8.00-$10.00	$10.00-$14.00	$16.00-$18.00
DESOTO	5.50- 8.50	7.00- 10.00	8.50- 12.00	17.50
LENNOX	7.50- 13.00	9.00- 14.00	13.00- 13.50	20.50- 35.00
MAYFAIR	7.50- 13.00	9.00- 14.00	13.00- 14.00	21.00- 35.00
PICK-MARK TWAIN	6.50- 9.00	8.50- 11.50	10.00- 12.50	17.50- 27.00
SHERATON-JEFFERSON	8.50- 11.00	12.00- 14.50	13.85- 18.00	28.00- 49.00
STATLER-HILTON	8.00- 11.50	11.00- 14.50	13.00 -15.00	29.50- 36.50
WARWICK	5.50- 8.00	8.50- 12.00	9.50- 12.00	

CONVENTION RESERVATION BUREAU
SOUTHERN MEDICAL ASSOCIATION
911 Locust Street, Room 406
Saint Louis 1, Missouri

Please reserve the following accommodations for the Southern Medical Association Meeting, October 31-November 3, 1960:

Hotel Preference	Kind of Accommodations Desired
1st Choice.....	.....Single room at $.....to $.....
2nd Choice.....	.....Double room at $.....to $.....
3rd Choice.....	.....Twin bedroom at $.....to $.....
	.....2-Room Suite at $.....to $.....
	.....Other type .....
Arrival Date.....	.....hour.....a.m.....p.m.
Departure Date.....	.....hour.....a.m.....p.m.

THE NAME OF EACH HOTEL GUEST MUST BE LISTED. Reservations cannot be made in any hotel unless two names are given for each double bedded room or twin bedded room. If this information is not given on your original application, the Convention Reservation Bureau must send you a card asking that you submit two names. This means unnecessary delay and lessens the possibility of assignment to the hotel of your choice.

Name of Occupant (s) (Please type or print)	Address
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Individual Requesting Reservations
(Please type or print)

NAME.....

ADDRESS.....

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CONVENTION RESERVATION BUREAU

Southern Medical Association

911 Locust Street, Room 406

Saint Louis 1, Missouri

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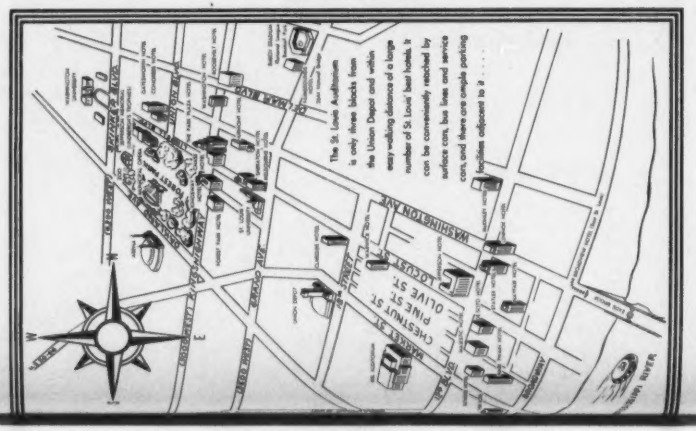
The St. Louis Auditorium is only three blocks from the Union Depot and within easy walking distance of a large number of St. Louis' best hotels. It can be conveniently reached by surface cars, bus lines and service cars, and there are ample parking facilities adjacent to it . . .
WASHINGTON AVE
LOCUST ST.
OLIVE ST.
PINE ST.
CHESTNUT ST.
MARKET ST.
BROADWAY
MISSISSIPPI RIVER

SOUTHERN MEDICAL NEWS

Continued from page 521

New additions to the medical staff of East End Memorial Hospital include Dr. Bluitt Landers, Jr., Birmingham, to practice neurosurgery; Dr. Percy Sullivan, Birmingham, to practice pediatrics; and Dr. George L. Ricketts, Jr., Springville, general practice.

Three members of the Department of Medicine of the University of Alabama Medical Center were elected to Associate Membership by the Board of Regents of the American College of Physicians. They are Drs. James F. Crenshaw, James A. Pittman, Jr., and H. Duke Thomas, all Assistant Professors.

Dr. Don Olson, Assistant Professor of Speech Pathology at the University of Alabama Medical Center, is the newly elected Vice-President of the Alabama Speech and Hearing Association.

ARKANSAS

The first woman pathologist ever to work in the Harvard Crime Laboratory is Dr. Betty Jane McClellan, North Little Rock. She performs autopsy examinations.

Dr. Lowry H. McDaniel, Tyronza, is Secretary-Treasurer of the Mid-South Postgraduate Medical Assembly.

Dr. Samuel B. Thompson, Little Rock, is Treasurer of the American Academy for Cerebral Palsy.

DISTRICT OF COLUMBIA

Dr. James Watt, Director of the National Heart Institute, PHS, has been appointed Special Assistant for Aging to the Secretary of Health, Education, and Welfare. Dr. Watt will continue to serve as Director of the Heart Institute.

Dr. Raymond T. Holden has been appointed Acting Medical Director and Administratior of Columbia Hospital for Women.

Dr. Marvin E. Perkins, former first Chief of the Bureau of Mental Health, has become Director of New York City's Community Mental Health Board. Dr. George W. Metcalf has succeeded Dr. Perkins as Chief of the Mental Health Bureau.

Dr. Edgar W. Davis, Clinical Professor of Surgery at Georgetown University School of Medicine, was elected President of the Southern Thoracic Surgical Association.

Dr. William P. Herbst was elected President of the Middle Atlantic Section of the American Urological Association and Dr. W. Dabney Jarmon was elected Secretary-Treasurer.

Dr. John D. Porterfield, Deputy Surgeon General of the United States Public Health Service, has been elected to another 3 year term on the Association's Executive Board.

Dr. Jesse Keene was re-elected President of the Public Interest Civic Association.

Dr. George Speck, specialist in obstetrics and gynecology, is the new President of the medical staff of Alexandria Hospital.

Major General William H. Powell, Jr., Assistant to the Surgeon General, USAF, was recently awarded the Legion of Merit, prior to his retirement, for his outstanding service to the United States while serving as Chief Medical Officer, Supreme Headquarters Allied Powers Europe, from July 3, 1957, to September 3, 1959.

The Academy of Medicine of Washington, D. C., has elected the following officers: Dr. Joseph H. Roe, President; Dr. Errett C. Albritton, Vice-President; Dr. Angus Griffin, Secretary; and Dr. Robert C. Cook, Treasurer.

Dr. William A. Howard is President of the Allergy Society of the District of Columbia. Serving with him are Dr. Harry A. Horstmann, Vice-President; and Dr. Audrey M. Connor, Secretary-Treasurer.

Dr. Helen M. Wallace, has been appointed Chief of Professional Training, Division of Health Services, Children's Bureau, Washington, D. C.

Dr. Lawrence J. Thomas is Treasurer of Phi Lambda Kappa, medical professional fraternity.

FLORIDA

Dr. Harold S. Kaufman, Miami, is an Associate Member of the International College of Surgeons.

Dr. Thomas E. Langley, Eustis, has been elected medical advisor to the Lake County Unit of the American Cancer Society for 1960.

Dr. Stanley E. Schwartz, Miami Beach, has been elected President of the Greater Miami Chapter of Phi Delta Epsilon national medical fraternity. Other officers include Dr. Seymour L. Alterman, Miami Beach, Vice-President; Dr. Morton L. Hammond, Miami, Secretary; and Dr. Milton E. Lesser, Miami Beach, Treasurer.

Dr. Hawley H. Seiler, Tampa, has been re-elected Secretary-Treasurer of the Southern Thoracic Surgical Association.

Dr. Lee E. Bransford, Sr., Jacksonville, has been honored by the local Downtown Lions Club for his work in the sight conservation program. Dr. Bransford is one of the founders of the Club.

Dr. Coy L. Lay has been elected Chairman of the Lakeland Cancer Committee. Serving as committee chairmen will be Drs. John P. Collins, Samuel J. Clark, Edgar Watson, and Frank H. Deland. All are from Lakeland.

Dr. H. C. Nelson, Jr., Miami, has been certified by the American Board of Surgery.

Dr. G. Thomas Samartino, Coral Gables, has been elected to membership in the American Academy of Orthopaedic Surgeons.

Officers of the Miami Orthopaedic Society are Dr. E. W. Cullipher, President; Dr. W. Stanley Weinkle, Vice-President; and Dr. William G. Aten, Secretary-Treasurer.

Dr. Robert V. Edwards, South Miami, and Dr. Samuel W. Page, Jr., Miami, have been elected Fellows of the American College of Physicians.

Dr. Cyrus E. Warden, Melbourne, has been elected President of the Brevard County Medical Society. Other officers include Dr. Willard H. Bennett, Titusville, President-Elect; Dr. Carl J. Arnold, Jr., Cocoa, Vice-President; Dr. John M. Gayden, Melbourne, Secretary; and Dr. Joseph C. Von Thron, Cocoa Beach, Treasurer.

Dr. Loral F. Gwaltney, has been installed as President of the Collier County Medical Society. Dr. John C. Garland is Vice-President; Dr. Ethel H. Trygstad, Secretary; and Dr. William J. Bailey, Treasurer. The doctors are all from Naples.

Dr. Harold S. Agnew, Arcadia, has been elected President of the DeSoto-Hardee-Glades County Medical Society. Dr. Elmer J. Schmierer, also of Arcadia, is Secretary-Treasurer.

Dr. Floyd K. Hurt has been installed as President of the Duval County Medical Society. Dr. Sidney Stillman is President-Elect; Dr. F. Gordon King, Vice-President; Dr. Albert Rood, Secretary; and Dr. Robert J. Brown, Treasurer. All are from Jacksonville.

New members of the Florida State Medical Association include: Dr. Joseph J. Bennett, West Hollywood; Dr. Donald J. Bradley, Pensacola; Dr. Santino J. Catanzaro, Ft. Lauderdale; Drs. John M. Cox and Robert E. Delgado, Orlando; Drs. Jefferson R. Edwards, Jr., and Woodrow G. Ellis, Pompano Beach; Drs. John H. Hirsh and W. Lewis Holder, Ft. Lauderdale; Dr. A. Ralph Monaco, Panama City; Dr. Brian K. Montgomery, Pensacola; Dr. O. Edwin Olsen, Orlando; Dr. Harvey Wiener, Hollywood; Dr. Stanley L. Rapaport, Fern Park; Dr. Juddson E. Shephard, Winter Park; and Dr. Roy L. Simon, Ft. Lauderdale.

Officers of the Greater Miami Radiological Society are Dr. Andre F. Capi, Hollywood, President; Dr. George P. Daurelle, Miami, Vice-President; and Dr. Donald H. Altman, Miami, Secretary-Treasurer.

Dr. Harriet Gillette, Chairman of the Department of Physical Medicine at the College of Medicine, University of Florida, has been elected a member of the Executive Committee of the American Academy for Cerebral Palsy.

Dr. A. E. Ogden, Coral Gables, has been certified as a Diplomate of the American Board of Surgery.

Dr. Francis T. Holland, Tallahassee, has been re-elected Chairman of the Florida Committee on Rural Health.

GEORGIA

Dr. W. P. Roche, Jr., Dublin, has been appointed a Consultant at the Veterans Administration Center in Dublin.

Officers of the medical staff of the Tanner Memorial Hospital in Carrolltown include: Dr. R. L. Sweeney, Chief of Staff; Dr. Harold L. McLendon, Vice-Chief of Staff; Dr. J. Harvey Beall, Secretary-Treasurer; Dr. Tom Reeve, Chief of Surgery; Dr. W. Steve Worthy, Chief of Obstetrics and Gynecology; Dr. E. V. Patrick, Chief of Medicine; Dr. E. C. Bass, Chief of Pediatrics; Dr. D. S. Reese, Chief of Eye, Ears, Nose, and Throat; and Dr. Phil C. Astin, Chief of Scientific Services. All are from Carrolltown.

New members of the Medical Association of Georgia are: Drs. William F. Bennett, Jr., Joseph N. Berry, Barbara Ann Brew, Ira A. Ferguson, Jr., Richard B. Heilman, E. Walter Hood, Conway W. Hunter, Jr., Frank M. Johnston, John S. Josey, Tom W. LeLand, Robert C. Schlant, Nanette K. Wenger, and Stephen C. Woodward, all of Atlanta; Dr. Julian Williams, Augusta; Dr. Walter S. Gresham, Bowdon; Dr. Jack Birge, Carrolltown; Dr. Louis D. Mahue, Dalton; Dr. Janet K. Johnson, Gainesville; Dr. Robert J. McCandliss, Milledgeville; Dr. Thomas H. Moss, Jr., Rome; Dr. David L. Branch, Jr., Valdosta; and Dr. Henry W. Harper, Jr., Washington; Dr. Oscar F. Whitman, Albany; Drs. Charles P. Adams, Margaret L. Brown, Henry C. Johnson, Jr., Sidney Olansky, Joel S. Steinberg, Peter D. Walz, and Lamar H. Walters, all of Atlanta; Drs. Mims C. Aultman and Hugh F. Smission, Jr., both of Augusta; Dr. James R. Thompson, Brunswick; Drs. Bryon H. Dunn, Albert H. Fregosi, Timothy Harden, Jr., Edward L. Johnson, Edwin H. McDowell, Jr., David L. Morgan, and Silas Angier Wills, all of Decatur; Dr. Ira H. Slade, Jr., Griffin; Dr. Harry R. Foster, Jr., Lithonia; Drs. Robert W. Oliver, Jr., and Michael H. Whittle, both of Lyons; Dr. Ralph A. Tillman, Pearson; and Dr. Milton G. Middleton, Thomasville.

Dr. M. Bedford Davis, Atlanta, has been elected a Fellow in the American College of Chest Physicians.

Dr. Alfred A. Weinstein, Atlanta, has been made President Emeritus of the Staff of Hughes Spalding Pavilion.

Dr. Sidney Olansky, Department of Medicine of Emory University, has been elected to the Board of Directors of the American Academy of Dermatology and Syphilology.

Dr. Thomas F. Sellers, Jr., has been promoted from Assistant Professor of Medicine at Emory University to Chairman of Preventive Medicine and Community Health. He will continue as Assistant Professor of Medicine as well.

KENTUCKY

Dr. Daniel B. McIlvoy, Jr., Bowling Green, has been named Vice-Chairman of the Kentucky Poison Control Committee.

Dr. Russell E. Teague, Louisville, Kentucky's Commissioner of Health, has been appointed by President Eisenhower to the 9 member National Water Pollution Control Advisory Board.

Two Lexington physicians, Drs. R. C. Morris and K. S. Phillips, are the newest members of the Kentucky State Medical Association.

Dr. Francis Massie, Lexington, has been elected President of the Southern Surgical Association.

Dr. Lytle Atherton, Louisville, is President of the Louisville Surgical Society. Other officers include Dr. Henry S. Collier, Vice-President; and Drs. Walter Hume, Jr., and Ludwig Segerberg, Executive Committee.

Seven Frankfort physicians have received awards for distinguished service to the King's Daughters' Hospital. Recognized for at least 22 years of service on the active staff were Drs. Joseph Barr, B. B. Baughman, W. P. Blackburn, L. L. Cull, Edward K. Martin, Grace Snyder, and W. S. Snyder, Jr.

The Jefferson County Medical Society has chosen Dr. George W. Pedigo, President; Dr. Daniel G. Costigan, President-Elect; Dr. Frank M. Gaines, Jr., First Vice-President; Dr. Louis Mitzlaff, Second Vice-Presi-

Continued on page 52

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**Deceased.

BOOK REVIEWS

Nutritional Diagnosis

By Grace A. Goldsmith, M.D., Professor of Medicine and Director, Nutrition-Metabolism Unit, Department of Medicine, Tulane University School of Medicine. 164 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1959. Price $5.50.

To many physicians the term "nutrition" has a very limited meaning with the thought that it includes only undernutrition in terms of calories and the vitamin deficiencies. The practicing physician so frequently does not think of the minerals in this area of the body's economy. The science of nutrition has made marked advances over the past couple of decades and much has appeared in the literature in this broad field. No physician, whether general practitioner or specialist, can disregard the many facets of nutrition which generally are taken for granted in the healthy, well-fed individual, but which must be given careful consideration in the person with systemic disease, who at times has marked disturbances in his tissue metabolism. Dr. Goldsmith, with long experience, not only in research in the field of nutrition, but with an extensive experience in the clinical aspects of nutrition and its disturbances, at the Charity Hospital in New Orleans, has distilled from the extensive and accumulated literature the knowledge which should be at hand for the practitioner of medicine. She has encompassed this in a small, very readable text, which brings the practical aspects up-to-date in easily understood language. The reviewer is sure that nowhere else can the practitioner of medicine find the information he needs in everyday practice, as well as in this small book.

Cardiac Arrest and Resuscitation

By Hugh E. Stephenson, Jr., M.D., Professor and Chairman, Department of Surgery, University of Missouri School of Medicine, Columbia, Missouri. 371 pages. St. Louis: C. V. Mosby Company, 1958. Price $12.00.

This is the most extensive book on the subject of cardiac arrest by a man who is most interested in the subject and has established a Cardiac Arrest Registry.

The history and incidence of cardiac arrest are presented first, followed by a chapter on the diagnosis of cardiac arrest. This chapter contains the key to the whole problem of cardiac arrest. I quote: "The delay in making a diagnosis of cardiac arrest (with its subsequent delay in instituting treatment) is responsible for approximately 85 per cent of the failures of resuscitation . . . Again, let us emphasize, more patients lose their chance for recovery during this crucial period between arrest and diagnosis than from any other aspect of the resuscitative procedure."

The etiology of cardiac arrest is covered as to physiologic and chemical causes as well as the situations in which cardiac arrest occurs. The management of cardiac arrest is presented both as to anatomic and pharmacologic management.

A most important chapter is the one on prevention of cardiac arrest which Dr. Stephenson calls the "most singular important aspect of the problem."

The last chapter is on long term neurologic sequelae, and closes the book with the plea to prevent these by early diagnosis, rapid establishment of respiration and adequate cardiac massage with use of hypothermia in the post-resusitative period.

Orthopaedics in General Practice

By W. H. Gervis, M.A., M.B., B.Ch., Cantab., F.R.C.S., Orthopaedic Surgeon West Kent Hospital, Maidstone, Kent and Sussex Hospital, Tunbridge Wells, Queen Victoria Hospital, East Grinstead. 116 pages. Springfield, Ill.; Charles C. Thomas, Publisher, 1959. Price $3.00.

Mr. Gervis has written a chatty book regarding pain in the neck and upper extremity, backache and foot pain. He has some provocative ideas including the usefulness of extension exercises for back pains whereas in this country, generally flexion exercises are used. He does have a rather interesting but short discussion on foot pain, particularly that due to flatfeet and has some good ideas regarding the etiology of flatfeet.

The illustrations in the book are thoughtful and well-done, and it will have a limited reading public among orthopaedic surgeons.

International Pharmacopoeia

First edition, Supplement. 224 pages. Geneva World Health Organization. New York: Columbia University Press, 1959. Price $5.00.

This monograph is a supplement to the International Pharmacopeia, first edition. The volume deals primarily with specifications for inclusion of drugs in the pharmacopeia. There are tables of doses for adults and children. Some new preparations have been added including certain hormonal preparations, antimalarials, and antibiotics. A very useful section of the book includes methods of preparation of isotonic solutions of 67 different substances.

Anesthesia for Infants and Children

By Robert M. Smith, Anesthesiologist, The Children's Medical Center, Boston, Mass., Assistant Clinical Professor of Anesthesia, Harvard Medical School. 418 pages. St. Louis: C. V. Mosby Company, 1959. Price $12.00.

This book is by one of the leading pediatric anesthesiologists in the United States.

The material is presented in a logical form. Subjects covered are basic, such as respiratory Physiology in children, Biology and Behavior, equipment used, technics used. Special technics such as hypothermia extracorporeal circulation are covered. Anesthetic problems for each of surgical specialities are covered. There is an excellent section on complications and mortality in

Pediatric Surgery and Anesthesia. Dr. Smith finds that the nonrebreathing technic is best in his hands, however he stresses that there are other safe and satisfactory methods as long as the basic problems are understood. His book helps one in understanding these problems.

This is an excellent book for the teaching of anesthesiology and also for the surgeon and pediatrician.

A Practice of Thoracic Surgery

By A. L. d'Abreu, Surgeon, Queen Elizabeth Hospital and the Children's Hospital, United Birmingham Hospitals, Consultant Adviser in Thoracic Surgery, Birmingham Regional Hospital Board. 605 pages. Baltimore: Williams & Wilkins Company, 1959. Price $19.00.

This is a well-written book which as the author says has deliberately selected the title "A Practice of Thoracic Surgery" rather than "The Practice of Thoracic Surgery" since this is primarily a description of his opinions and method of management of certain specific cases. The anatomic and physiologic considerations of the book are well-done as is the surgery for pyogenic infection. The section on pulmonary tuberculosis seems to dwell a little bit too much on the older conservative approach to the disease and the indications for resections of tuberculous lesions seem to be a little different than do the present day indications in the United States. It is apparent from the book that still more collapse procedures are being done in England than in our country and for the young thoracic surgeon this might be a little misleading. The section on surgery for congenital heart lesions has a very good description of angiocardiography by Dr. Astly, and cardiac catheterization is very well presented by Dr. Davidson. The operations and the mortality rates for congenital cyanotic and acyanotic heart disease are well covered though there is a tendency to use more of the blind procedures than are used at this time in this country. The sections on disease of the esophagus and miscellaneous conditions are very well done as is thoraco-abdominal surgery.

This is a very enjoyable book which is easy to read. To some readers the negative reproductions of x-rays do not yield as clear a picture as do positive prints; this is probably done for economic reasons in this particular book, since all x-rays are negative reproductions. Also various instruments liked and used by Dr. d'Abreu are not available in this country.

Dictionary of Medical Discoveries: Who and When

By J. E. Schmidt, M.D. 555 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1959. Price $14.75.

The author had an interesting thought in collecting the material for this book. The introduction states that there are more than 6,000 entries in the book which thus represents a storehouse of information. The item which represents the subject of interest to the reader appears in boldface type and beneath it appears a short statement of the scientist who first described this, the years of his life, and the date at which the topic was first recorded. For example, "Electrocardiograph, invention of, Willem Einthoven, Dutch physiologist, 1860-1927, invented the electrocardiograph in 1903, . . ." Another example, "Schizophrenia, insulin shock, treatment of, Manfred Sakel, American psychiatrist, 1900- , introduced the use of insulin shock in the treatment of mental disorders especially schizophrenia, in 1929 . . ."

Indeed this is a remarkable collection of medical discoveries and an excellent reference book for any medical reader who is interested in the historical aspects of medicine and certainly of value to the medical writer who has occasion to use historical references.

The author is to be commended for this idea.

Systemic Lupus Erythematosus

Editors George Baehr, M.D., and Paul Klemperer, M.D. A Mount Sinai Hospital Monograph. 82 pages. New York: Grune & Stratton, Inc., 1959. Price $3.75.

This represents a monograph on symposium by the members of the staff of Mount Sinai Hospital, particularly interested in the topic under discussion. It is edited by Doctors Baehr and Klemperer, pioneers in the study of the many facets of systemic lupus.

In this symposium which deals with the pathology of systemic lupus, the nature and pathogenesis of the L.E. cell, the hematologic findings in systemic lupus, the clinical features of the disease, its manifestations in childhood, and the therapy of systemic lupus make up a valuable summary of the disease as seen through the eyes of the Mount Sinai group.

Anyone interested in this disease will find an excellent review of many of its facets.

Dictionary of Medical Slang

By J. E. Schmidt, M.D. 207 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1959. Price $6.75.

This is an unusual book. The author has for many years collected words and phrases in slang with a medical connotation or orientation. The reader will be astounded at the number and variety of items listed in this book. It is a curiosity item.

A Synopsis of Skin Diseases

By Bethel Solomons, Jun. M.A., M.D., F.R.C.P.I., Consultant Dermatologist, Chelmsford and Essex General Hospital. 272 pages. Baltimore: Williams & Wilkins Company, 1959. Price $6.75.

This is a small volume labeled "A Synopsis of Skin Diseases." Apparently it is one of a series of similar books on various subjects. In the words of the author it is intended for the busy practitioners, for those who have to review the subject rapidly and also for the student about to take his final examination.

The book is essentially an outline in which cutaneous conditions are divided into various categories, viral diseases, disturbances of pigmentation, tumors, etc. In this way subjects may be quickly reviewed. Many topics are covered in a few sentences. There are no photographs or bibliography. It does have tables of concentrations and vehicles to be used in patch testing and a small formulary.

This synopsis probably would be most useful for practitioners who would want a quick differential diagnosis of a subject, as for example bullous diseases, and for students or residents taking examinations.

Southern Medical Association Group

Disability Plan Meets A Great Need

Few members realize the tremendous job being done by the officially sponsored Group Disability Plan underwritten by Continental Casualty Company. A report to the Insurance Committee at a recent meeting in Birmingham revealed that the number of members enrolled in the plan has steadily grown each year until now, almost 5,000 members are enrolled. Claims incurred have totaled over two million dollars since the plan was installed. As of now, disability benefits are being paid to disabled SMA members at the rate of more than $40,000 per month. This definitely proves that the Group Disability Plan is serving a great need and is one of the outstanding advantages of membership in the Southern Medical Association.

In order to more adequately meet the need for higher indemnities, approval was given to Continental's offer to increase the maximum available monthly indemnity from $400 to $600. These higher benefits of $500 or $600 per month are available to members under age sixty who are in good health. After it is issued, however, the coverage may be carried to age seventy.

Members presently insured in the SMA Plan for $400 per month or less may apply for increased benefits up to $600 per month. Members under age sixty who are not now insured in the SMA Plan are invited to apply for coverage up to $600 per month. The history of these professional group plans has proved that the more members there are enrolled in the plan, the more efficiently it operates. If a 75% enrollment can be attained, it is reasonably sure that the benefits could be increased or the premiums could be reduced. Certainly, the performance record of this plan merits the confidence and support of all eligible members. Complete details on this increased benefits plan will be mailed shortly.

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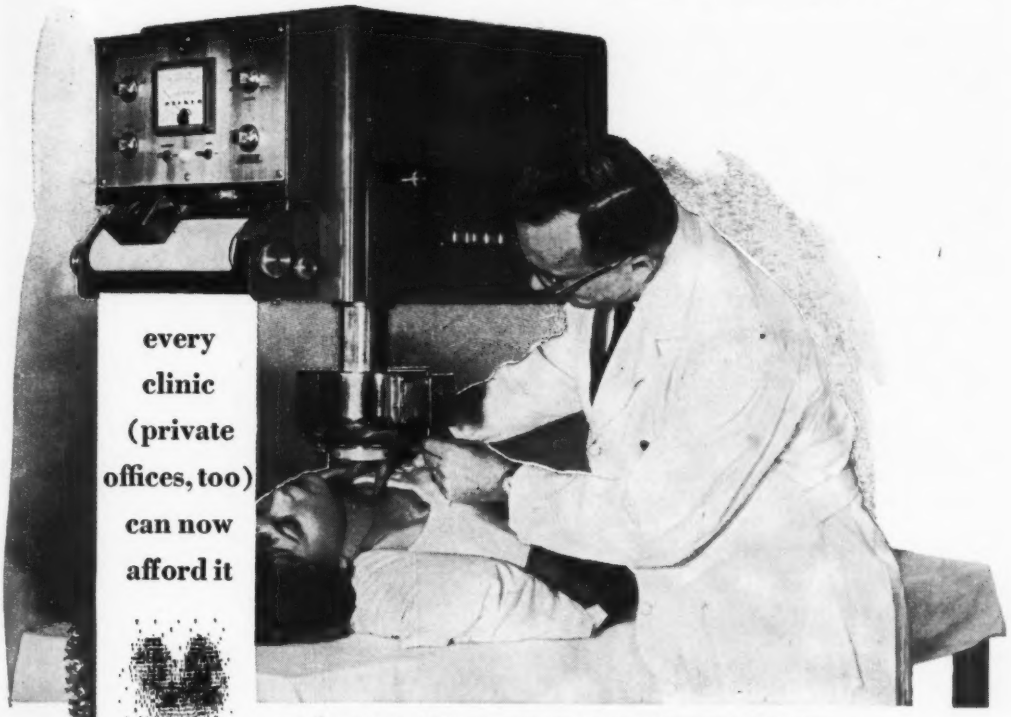

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Continued from page 526

dent; Dr. William E. Pugh, Secretary; Dr. Walter I. Hume, Jr., Treasurer; and Drs. J. Ray Bryant and Grover B. Sanders, Judicial Council members. All are Louisville physicians.

Dr. Nina Kateryniuk is the new Chief of Staff at Central State Hospital in Lakeland.

Dr. Raymond Myers, Dean of the University of Louisville Dental School, has been elected President of the Southern Conference of Dental Deans.

Dr. Dorothy Holtgrave, Louisville, is the new Director of Communicable Disease Control of the Louisville-Jefferson County Health Department. Dr. Holtgrave will continue her private practice.

Dr. William P. Peak, Louisville, is President of the Kentucky Chapter, Arthritis and Rheumatism Foundation.

Dr. Kingsley M. Stevens has joined the staff of the College of Medicine, University of Kentucky, as Assistant Professor of Medicine.

New members of the Kentucky State Medical Association are Dr. Robert H. Shipp, Shelbyville; Dr. Hubert F. Sturges, Crestwood; Dr. Horace W. Addams, St. Matthews; and Drs. Ferrell C. Lowrey, Jr., and Leslie Van Nostrand, both of Louisville.

LOUISIANA

The following New Orleans doctors were elected to office in the Academy of General Practice: Dr. Francis Nicolle, President of the First District and Secretary of the State Association; Dr. Esmond Fatter, Alternate Delegate to the National Assembly; Dr. Bruno F. Mancuso, Director of the First District; Dr. I. L. Fontenelle, Secretary of the First District; and Dr. Charles J. Moseley who continues as Alternate Director of the First District.

Dr. B. Bernard Weinstein, New Orleans, has been made Chairman of the Board of Governors of the International Fertility Association. Dr. Weinstein previously served as President of the Society and as a member of the Board of Directors.

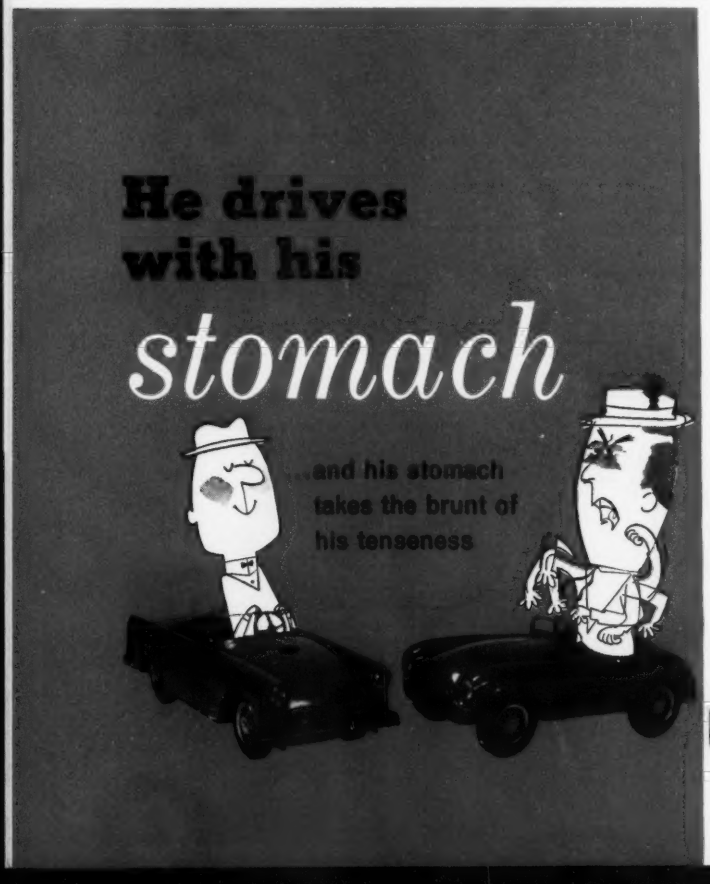
Dr. Daniel C. Riordan, Assistant Professor of Clinical Orthopedics at the Tulane University School of Medicine, has been installed as President of the American Society for Surgery of the Hand.

New officers of the Orleans Parish Medical Society are Dr. J. Theo Brierre, President-Elect; Dr. John Oakley, First Vice-President; Dr. J. Morgan Lyons, Second Vice-President; Dr. John Kron, Third Vice-President; Dr. C. F. Bellone, Secretary; Dr. Spencer B. McNair, Treasurer; Dr. John J. Archinard, Librarian; Drs. A. N. Sam Houston and W. Charles Miller, board members for a 2 year term.

Dr. L. J. Dubos, New Orleans, has been unanimously elected to honorary membership in the Orleans Parish Medical Society.

Dr. Gene L. Usdin, Assistant Professor of Clinical Psychiatry at the Tulane University School of Medicine, has been appointed to the board of psychiatric consultants to a study of mental illness and the law.

Continued on page 60



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quiets "nervous," spastic stomo

Butibel provides the efficient sedati of BUTISOL Sodium® butabarbi sodium 15 mg. and the antispasmo effect of natural extract of bellado 15 mg. [per tablet or 5 cc.]

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EACH Solfo-serpine tablet (yellow and embossed with figure of snake) contains 0.06 mg. reserpine, ¼ gr. phenobarbital, and ½ gr. colloidal sulfur.
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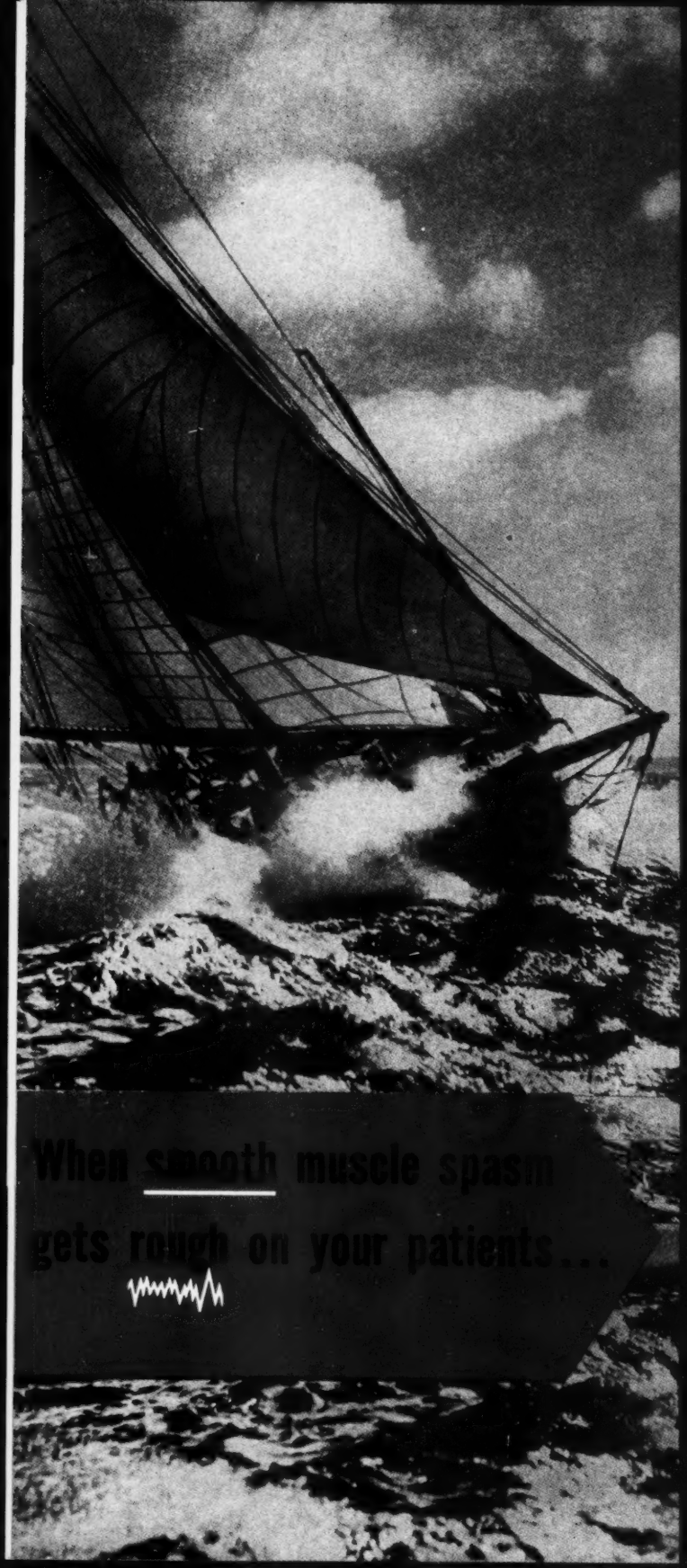

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Hyoscine hydrobromide 0.0065 mg.	0.01
Phenobarbital (¼ gr.) 16.2 mg.	(¾ gr.) 4

Prescribed by more physi
than any other antispasm

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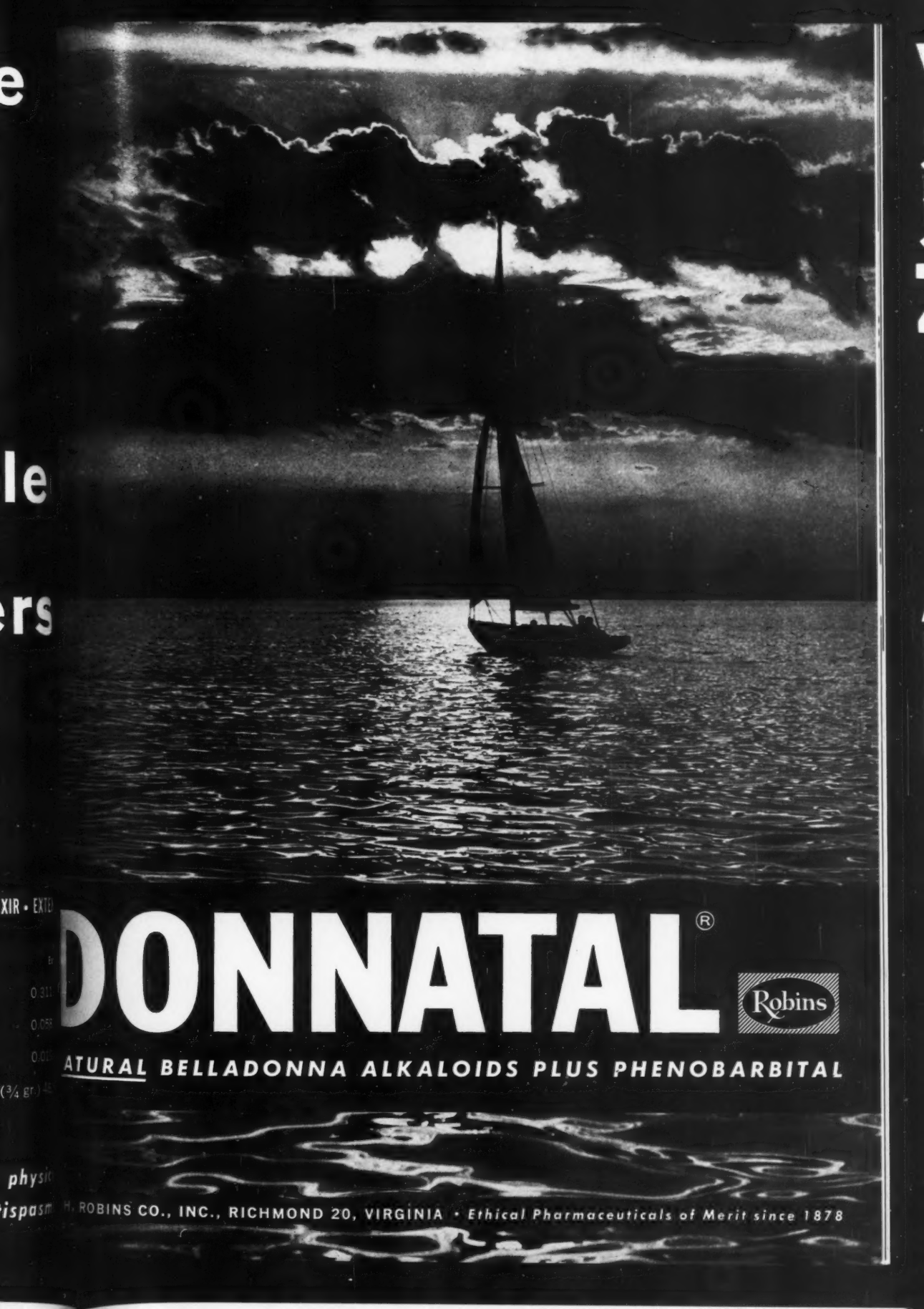
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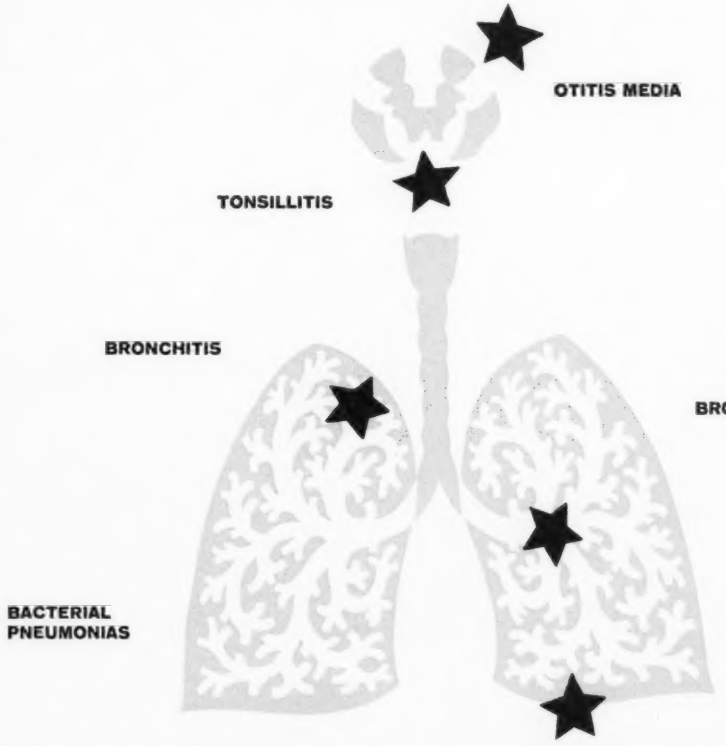

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"...outstanding advantages over many previously accepted chemotherapeutic and antibiotic agents"[1]

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effective perorally against the majority of common infections caused by pathogenic bacteria including the antibiotic-resistant staphylococci

ALTAFUR is available in tablets of 250 mg. (adult) and 50 mg. (pediatric), bottles of 20 and 100.

1. Lysaught, J. N., and Cleaver, W.: Proceedings of the Detroit Symposium on Antibacterial Therapy (Michigan and Wayne County Academies of General Practice, Detroit, Sept. 12, 1959).

THE NITROFURANS . . . a *unique* class of antimicrobials

EATON LABORATORIES, NORWICH, NEW YORK

in senile agitation, Thorazine®,
brand of chlorpromazine
one of the fundamental drugs in medicine, can control the agitated, belligerent patient and help her live a composed and useful life.

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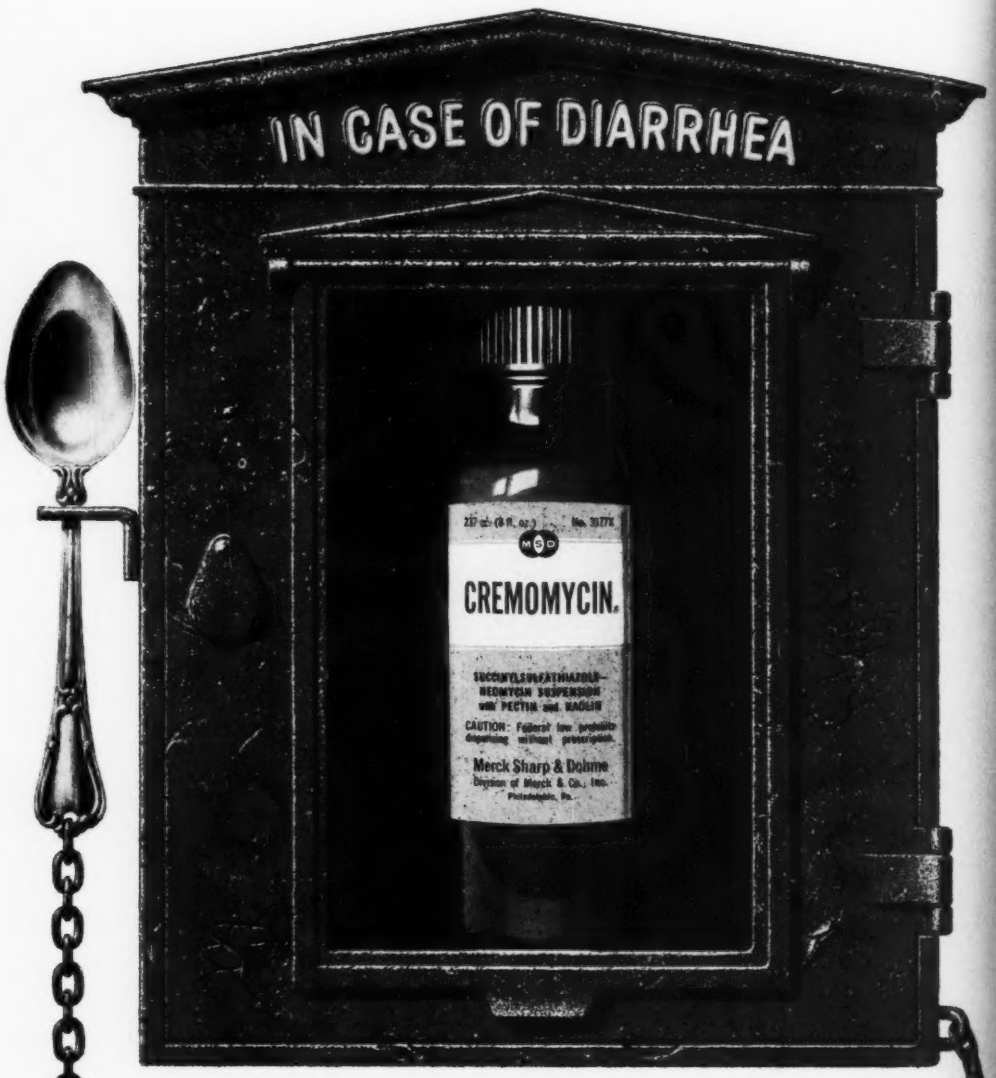

Cremomycin® provides rapid relief of virtually all diarrheas

NEOMYCIN—rapidly bactericidal against most intestinal pathogens, but relatively ineffective against certain diarrhea-causing organisms.

SULFASUXIDINE® (succinylsulfathiazole)—an ideal adjunct to neomycin because it is highly effective against Clostridia and certain other neomycin-resistant organisms.

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Pabirin

Continued from page 52

The study is to be conducted by the American Bar Foundation under a grant from the National Institutes of Health.

Dr. William W. Frye, Vice-President of Louisiana State University, Dean of the School of Medicine and Professor of Tropical Medicine, has been chosen President-Elect of the American Society of Tropical Medicine and Hygiene.

Dr. J. D. Russ, New Orleans, has been named Secretary of the American Academy for Cerebral Palsy.

Dr. Willard W. Wirth, New Orleans, has been elected President of the New Orleans Area Council, Boy Scouts of America.

Dr. John H. Seabury, New Orleans, has been elected President of the Southern Chapter of the American College of Chest Physicians.

Officers of the Mercy Hospital staff in New Orleans include Dr. Dennis H. Groome, President; Dr. Leon Hart, Vice-President; Dr. James Decuers, Secretary; and Dr. Hanckes Klein, Treasurer.

Dr. Max M. Green is President of the Hotel Dieu medical staff in New Orleans. Serving with him are Dr. George M. Haik, Vice-President and President-Elect; and Dr. Lucien C. Delery, Secretary-Treasurer.

Two new appointments at Touro Infirmary in New Orleans include Dr. Harry Meyer, Chief of the Department of Obstetrics, and Dr. M. D. Steiner, Chief of the Department of Gynecology.

Dr. Joseph R. Seelig was elected First Vice-President of the New Orleans Dental Association.

Officers of the New Orleans Academy of Pathology include Dr. G. M. Carrera, President; Dr. Jack Strong, Vice-President; and Dr. Friedrichs Harris, Secretary-Treasurer.

Dr. Henry D. Ogden, New Orleans, is President of a new society, the American Association for the Study of Headache.

MARYLAND

Drs. Barbara Williams and Erving Hardy have been appointed to the Easton Memorial Hospital staff in Easton.

Among the members of the consulting editorial board of the new *Journal of Nuclear Medicine* is Captain E. Richard King, MC, USN, U. S. Naval Hospital, Bethesda.

Officers of the Washington County Medical Society are Dr. William T. Layman, President; Dr. Dalton M. Welty, Vice-President; and Dr. Ernest F. Poole, Secretary-Treasurer. The physicians are all from Hagerstown.

Dr. Harold B. Plummer, Preston, has been chosen "Physician of the Year" by the Maryland Academy of General Practice.

Officers of the Maryland Academy of General Practice include Dr. Walter A. Anderson, Baltimore,

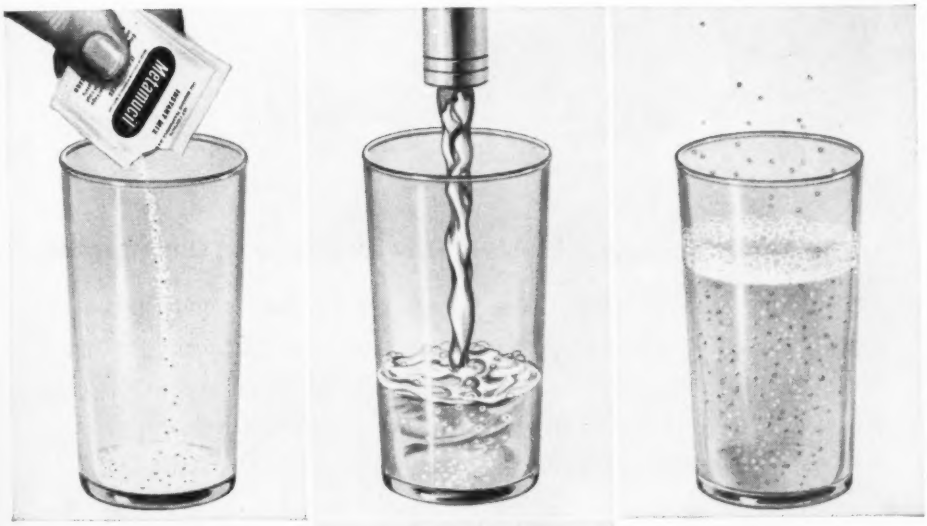
Continued on page 64

NEW FROM

SEARLE

INSTANT MIX METAMUCIL®

Psyllium hydrophilic mucilloid with citric acid and sodium bicarbonate



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add cool water slowly... it's instantly mixed

all the advantages of smoothage therapy in the relief and correction of constipation

- stimulates normal peristalsis
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and it's EFFERVESCENT!

- convenient, premeasured-dose packets
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SERPASIL®-ESIDRIX®

potentiated antihypertensive now available in 2 strengths

To meet the needs of patients who require greater diuretic-antihypertensive activity, Serpasil-Esidrix is now made available in a combination tablet containing **50 mg. Esidrix** and 0.1 mg. Serpasil. This tablet, Serpasil-Esidrix #2, will help you control high blood pressure in more patients. With Serpasil-Esidrix #2, you can expect a quick response: blood pressure usually begins to drop during the first few days of therapy. Excess fluid is also rapidly eliminated. And you give patients the additional benefits of Serpasil: control of tachycardia and relief of anxiety.

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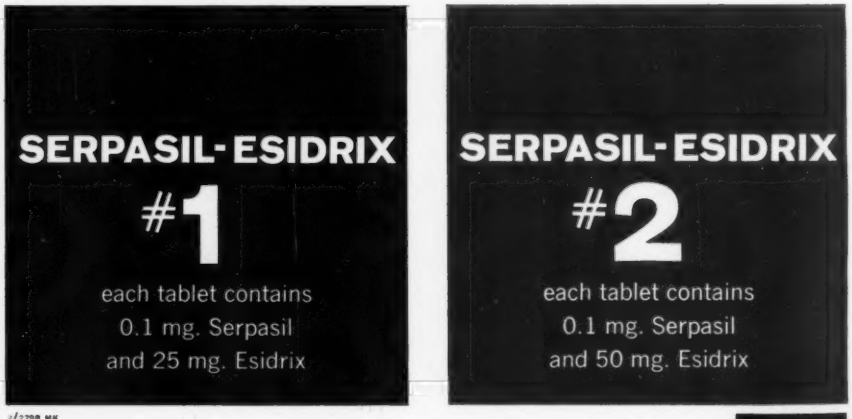

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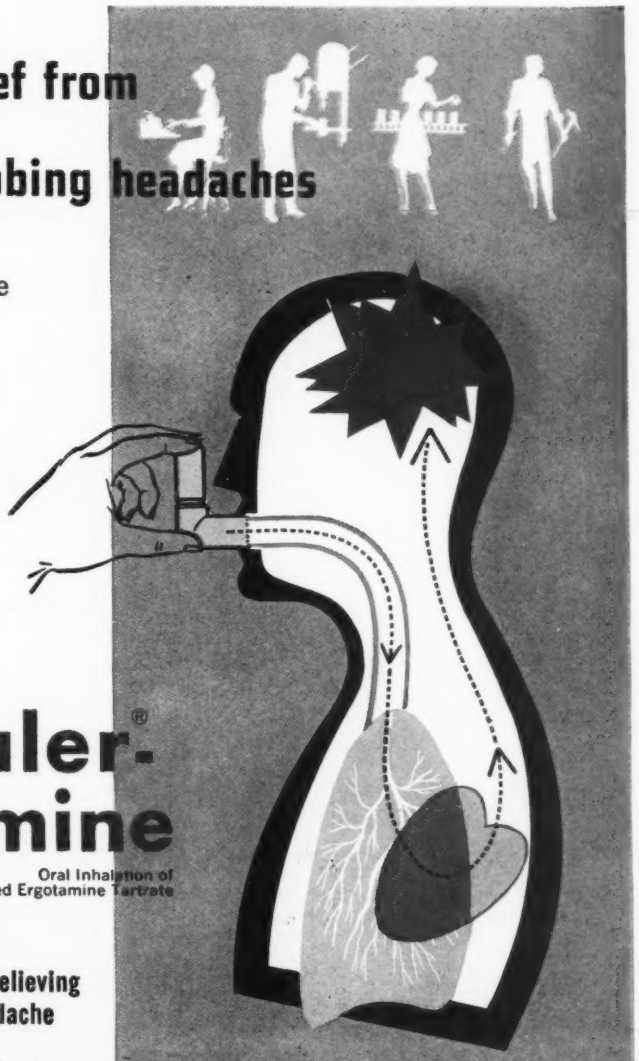
SUMMIT, N. J.

on-the-go relief from recurrent throbbing headaches

including migraine syndromes, other vascular headaches, histaminic cephalalgia, and occipital neuralgia



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In 2.5 cc. stainless steel vial (50 doses) with plastic oral adapter. Each depression of metering valve delivers 0.36 mg. ergotamine tartrate self propelled from the oral adapter.

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...depresses appetite...elevates mood...eases tensions of dieting...*without* overstimulation, insomnia, or barbiturate hangover.

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Each coated tablet (pink) contains: meprobamate, 400 mg.; d-amphetamine sulfate, 5 mg.
Dosage: One tablet one-half to one hour before each meal.

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Continued from page 60

Dr. Andrew C. Mitchell, Salisbury, President-Elect; Dr. Charles P. Crimy, Baltimore, Secretary; Dr. Harry L. Knipp, Baltimore, Treasurer; and Dr. George A. Moulton, Jr., Westminster, Dr. Page C. Jett, Prince Frederick, and Dr. Donald F. Bartley, Easton, Vice-Presidents.

Dr. Jacob H. Conn, Assistant Professor of Psychiatry at Johns Hopkins University Medical School, has been elected President of the Society for Clinical and Experimental Hypnosis. Dr. Conn has also been named a Diplomate of the American Board of Child Psychiatry and a Diplomate of the American Board of Medical Hypnosis.

A new junior member of the American Society of Anesthesiology is Dr. Richard B. Salsitz, Rockville; a new active member is Dr. Heinrich J. Losemann, Baltimore.

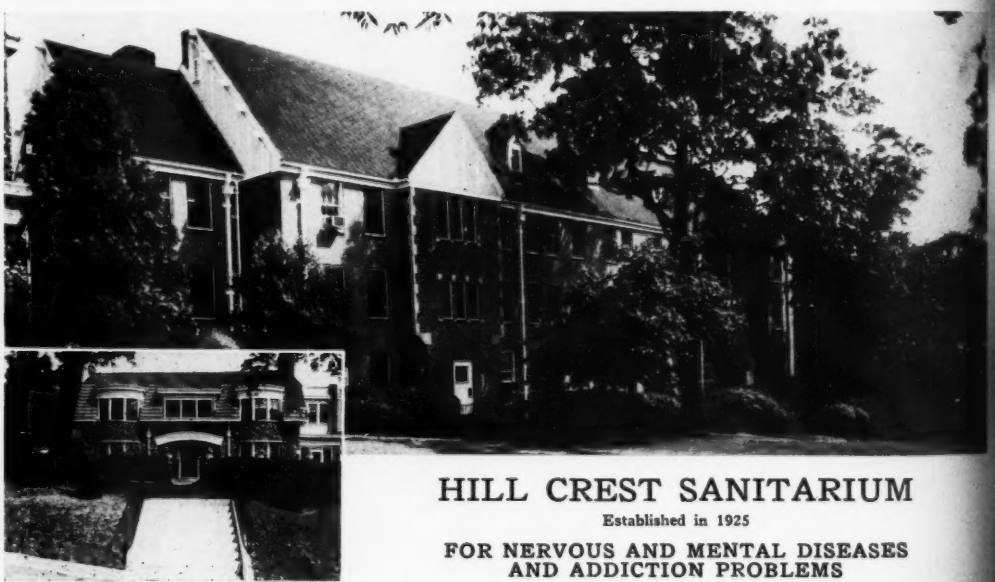
The following Baltimore physicians were named Fellows of the New York Academy of Sciences: Drs. Samuel P. Asper, Jr., David Bodian, Carlo Bruni, Francis P. Chinard, and Richard H. Shepard.

Dr. H. G. Reeves, Baltimore, has been certified by the American Board of Surgery.

MISSISSIPPI

New members of the Mississippi State Medical Association are Dr. Myron L. Arrington, Prentiss; Dr. Kirby K. Bryant, Jr., Mantachie; Dr. Joe T. Downard, Laurel; Dr. William R. Eure, Bay Springs; Dr. Jerry A.

Continued on page 68



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HILL CREST SANITARIUM
Established in 1925
FOR NERVOUS AND MENTAL DISEASES
AND ADDICTION PROBLEMS

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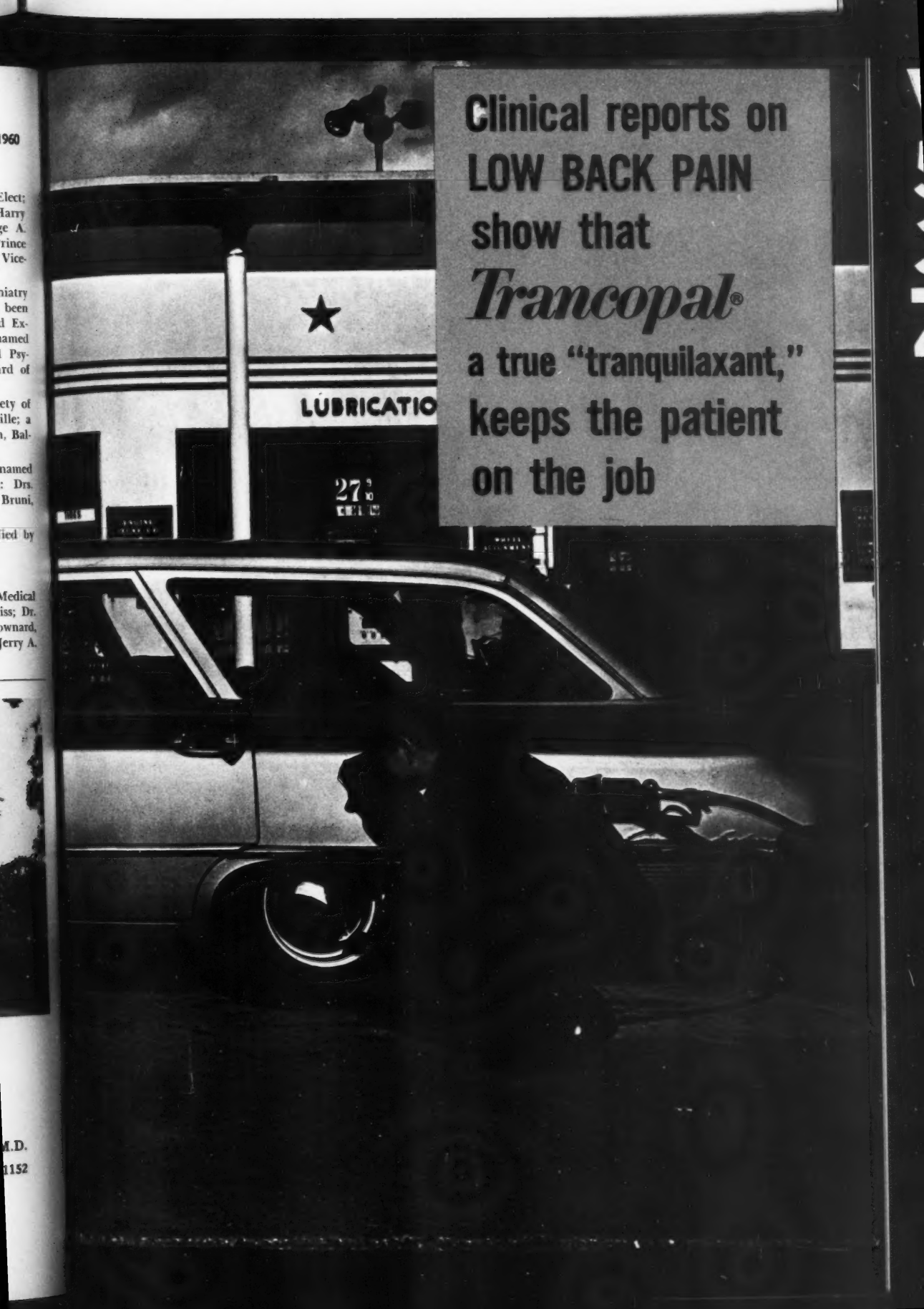
Clinical reports on
LOW BACK PAIN
show that
Trancopal®
a true "tranquilaxant,"
keeps the patient
on the job
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A TRUE "TRANQUILAXANT"

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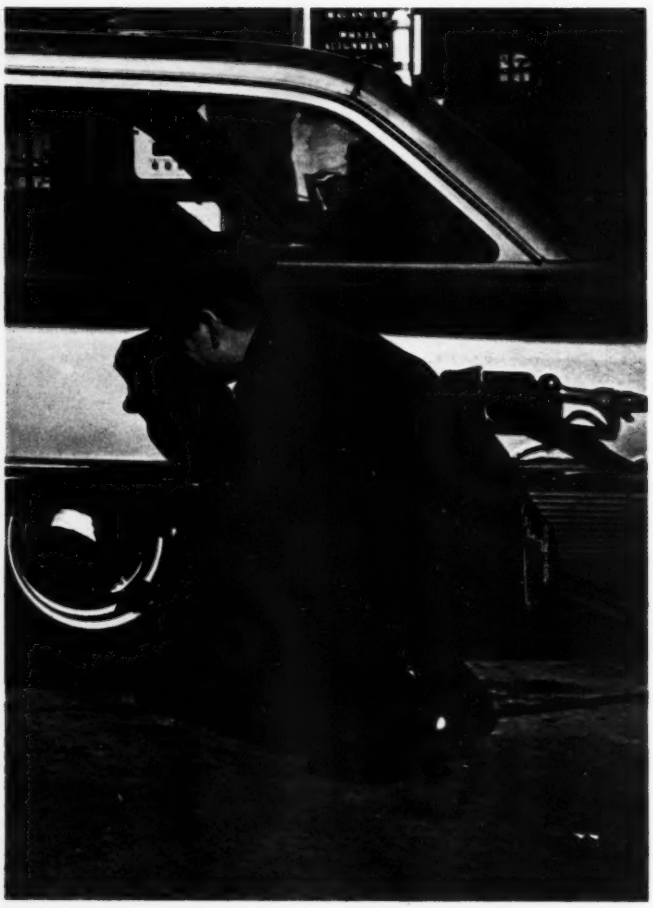

relaxes skeletal muscl… spasm so the patien… can continue to wor…

Clinical experience shows that Trancopal will … able your patients with low back pain to … going strong. Lichtman[1] reports that 310 of … 331 patients treated with Trancopal obtai… satisfactory relief. These patients were suffer… from low back pain, stiff neck, postoperat… muscle spasm or other skeletal muscle spas… associated with trauma, bursitis, osteoarthri… and rheumatoid arthritis. Mullin and Epifan… reported that Trancopal brought relief to all of 3… patients with skeletal muscle spasm. In thes… patients, who had suffered from trauma, bursit… rheumatoid arthritis, osteoarthritis, and interv… tebral disc syndrome, the effect of Trancopal wa… ". . . excellent and prompt . . ."[2] Gruenberg[3] ob… tained marked relief with Trancopal in 258 of 30… patients with low back pain, torticollis, arthri… and other conditions associated with skelet… muscle spasm. Moderate relief was obtained … an additional group of 28 patients. Trancopal … a true "tranquilaxant" because "It combines th… properties of tranquilization and skeletal muscl… relaxation with no concomitant change in norm… consciousness."[4] Side effects have been few an… minor — and in no case were they serious enough … to warrant discontinuing the use of Trancopal. … "Trancopal is exceptionally safe for clinical use.

lieves anxiety and tension so the patient can carry on

Trancopal is also an effective agent for patients in anxiety and tension states. According to recent clinical reports,[1,5] it calms the patients but allows them to continue their work or other activity. Indeed, Lichtman found that his patients with anxiety ". . . were in many instances able to continue their normal activities where previously they had been considerably restricted . . ."[1] He observed that Trancopal brought good to excellent relief to 114 of 120 patients in anxiety states. Ganz,[5] who noted good to excellent relief in 32 of 35 patients with globus hystericus, and in his entire series of 100 patients in anxiety or tension states, comments: "Chlormethazanone [Trancopal], by relieving the psychogenic symptoms, allows the patient to use his energies in a more productive manner in overcoming his basic problems."[5]

Relieves dysmenorrhea — Trancopal has also proved to be a useful medication in the treatment of patients with dysmenorrhea,[1,4,6] probably producing its effect ". . . by means of a combination of muscle relaxant and tranquilizing actions."[4]

Indications

Musculoskeletal disorders		Psychogenic disorders
Low back pain (lumbago)	Ankle sprain, tennis elbow	Dysmenorrhea
Neck pain (torticollis)	Osteoarthritis	Premenstrual tension
Bursitis	Rheumatoid arthritis	Anxiety and tension states
Fibrositis	Disc syndrome	Asthma
Myositis	Postoperative muscle spasm	Angina pectoris
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Dosage: Adults, 100 or 200 mg. orally three or four times daily. Relief of symptoms generally occurs promptly and lasts from four to six hours.

How Supplied: Trancopal Caplets® 100 mg. (peach colored, scored) and 200 mg. (green colored, scored), bottles of 100.

References: 1. Lichtman, A. L.: Kentucky Acad. Gen. Pract. J. 4:28, Oct., 1958. 2. Mullin, W. G., and Epifano, Leonard: Am. Pract. & Digest Treat. 2:1743, Oct., 1959. 3. Gruenberg, Friedrich: Current Therap. Res. 2:1, Jan., 1960. 4. Shanaphy, J. F.: Current Therap. Res. 1:59, Oct., 1959. 5. Ganz, S. E.: J. Indiana M. A. 52:1134, July, 1959. 6. Stough, A. R.: J. Oklahoma M. A. 52:575, Sept., 1959.

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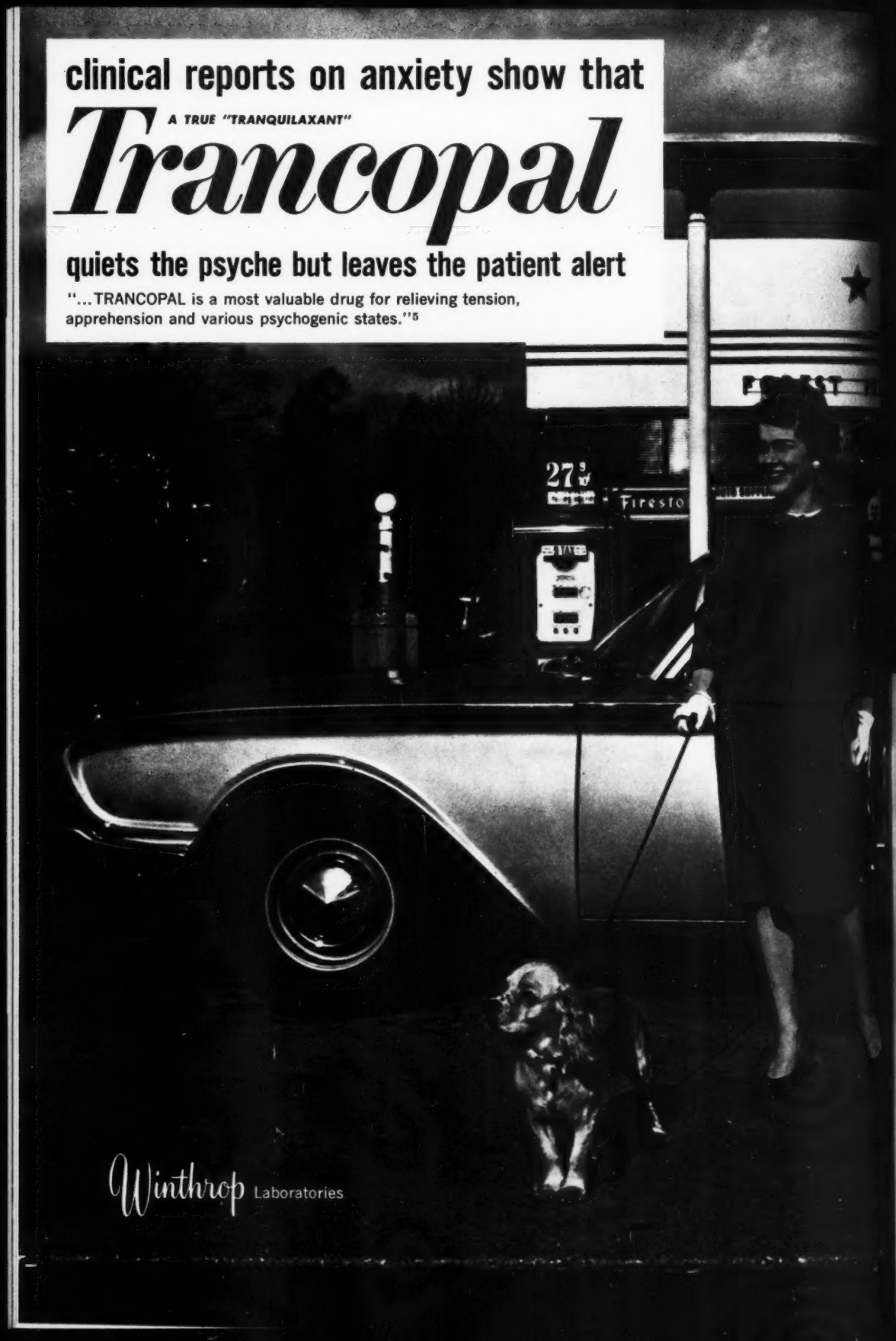
clinical reports on anxiety show that
A TRUE "TRANQUILAXANT"
Trancopal
quiets the psyche but leaves the patient alert
"...TRANCOPAL is a most valuable drug for relieving tension, apprehension and various psychogenic states."5
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in
hyperacidity and
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as reactive in tablet form . . .

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Dihydroxy aluminum aminoacetate

The superiority of Alglyn (dihydroxy aluminum aminoacetate) as an antacid over ordinary aluminum preparations is quite pronounced. Not only do Alglyn Tablets act as rapidly as aluminum hydroxide gels and magmas, but they maintain a much more effective pH for a longer time (see chart).

Furthermore, Alglyn Tablets are decidedly superior when antacid-belladonna therapy is indicated. Ordinary aluminum preparations may actually *ad*sorb as much as 80% of the spasmolytic drug, as compared to only 7% for Alglyn Tablets. In addition, Alglyn contains no sodium and less aluminum.

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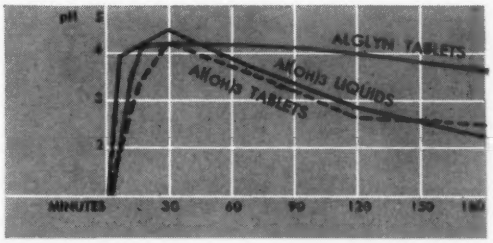

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prescribe

CAL-O-B

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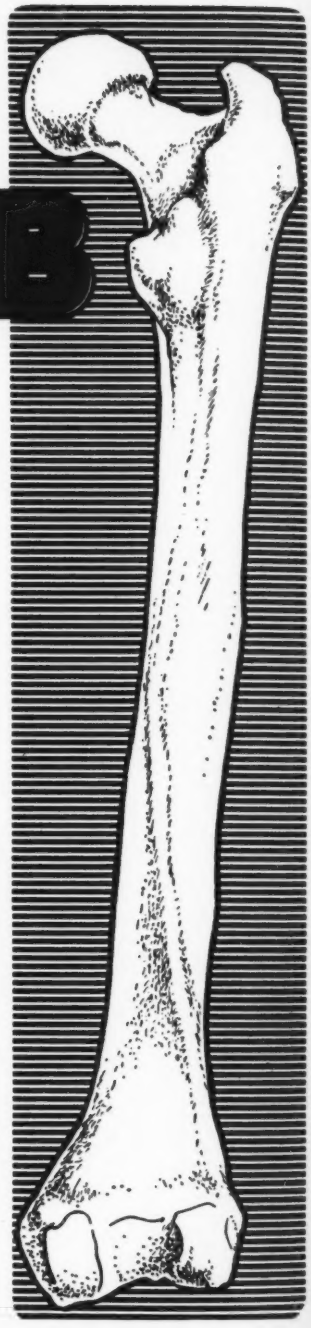

because calcium glycerophosphate provides uniquely assimilable calcium and phosphorus.

● Cal-O-B calcium produces greater calcium deposition in bone than other commonly used

phosphated or phosphorus-free calcium compounds. It is completely soluble and assimilable throughout the entire pH range of the G.I.

tract. Cal-O-B Tablets

also supply vitamins D, B_6 and C with iron and 12 trace minerals.

Each Tablet Contains:

Calcium Glycerophosphate	500 mg.
Ferrous Gluconate	200 mg.
Vitamin D_2 (Calciferol)	1000 units
Pyridoxine Hydrochloride	1 mg.
Ascorbic Acid	50 mg.
Twelve Trace Minerals	7.83 mg.

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DECLOMYCIN® NOTES:

Demethylchlortetracycline Lederle

pathogen

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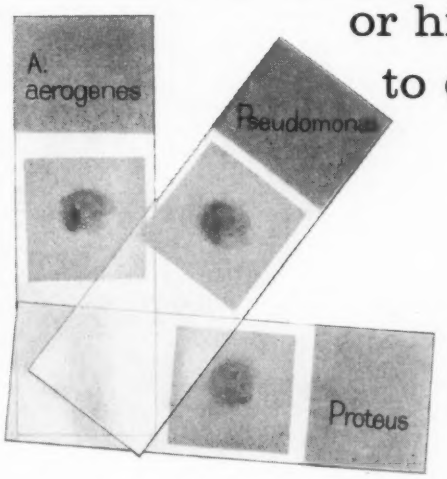
In addition to the expected broad-spectrum range of effectiveness, DECLOMYCIN has demonstrated activity against strains of Pseudomonas, Proteus and A. aerogenes[1-5] unresponsive or highly refractory to other antibiotics.



1. Department of Clinical Investigation, Lederle Laboratories, F. M. Phillips, Director. Interim Report on Clinical and Pharmacologic Investigations. 2. Finland, M.; Hirsch, H. A., and Kunin, C. M.: Read at Seventh Annual Antibiotics Symposium, Washington, D. C., November 5, 1959. 3. Hirsch, H. A.; Kunin, C. M., and Finland, M.: **München. med. Wchnschr.** To be published. 4. Roberts, M. S.; Seneca, H., and Lattimer, J. K.: Read at Seventh Annual Antibiotics Symposium, Washington, D. C., November 5, 1959. 5. Vineyard, J. P.; Hogan, J., and Sanford, J. P.: **Ibid.**

Capsules, 150 mg.—Pediatric Drops, 60 mg./cc. — Oral Suspension, 75 mg./5 cc. tsp.

GREATER ACTIVITY...FAR LESS ANTIBIOTIC...SUSTAINED-PEAK CONTROL..."EXTRA-DAY" PROTECTION AGAINST RELAPSE

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, N. Y

Continued from page 64

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Dr. A. L. Gray, Jackson, Executive Officer of the Mississippi State Board of Health, has been appointed by the U. S. Surgeon General to serve on a newly-formed advisory committee on venereal disease control.

Dr. Omar Simmons, Newton, is President of the Mid-South Postgraduate Medical Assembly and Dr. Thomas G. Ross, Jackson, is Vice-President.

MISSOURI

Officers of the Medical Council of the Metropolitan of Greater Kansas City are Dr. William W. Abrams, Chairman; Dr. John F. Bowser, Vice-Chairman; and Dr. Reinhardt D. Dwyer, Secretary.

The surgical staff of St. John's Hospital in Joplin has elected Dr. Lewis H. Ferguson, Jr., as Chief of the Surgical Service.

Dr. Richard H. Kiene, Kansas City, has been elected President of the Kansas City Southwest Clinical Society.

The International College of Surgeons has elected Dr. Donald M. Dowell, Chillicothe, as a Vice Regent for Missouri.

Continued on page 78

a logical combination for appetite suppression

meprobamate *plus* d-amphetamine

. . . suppresses appetite . . . elevates mood
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Each coated tablet (pink) contains: meprobamate, 400 mg.; d-amphetamine sulfate, 5 mg.
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for the tense and nervous patient

relief comes fast and comfortably

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—does not impair mental efficiency, motor control, or normal behavior.

Usual Dosage: One or two 400 mg. tablets t.i.d.

Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets or as MEPROTABS*—400 mg. *unmarked,* coated tablets.

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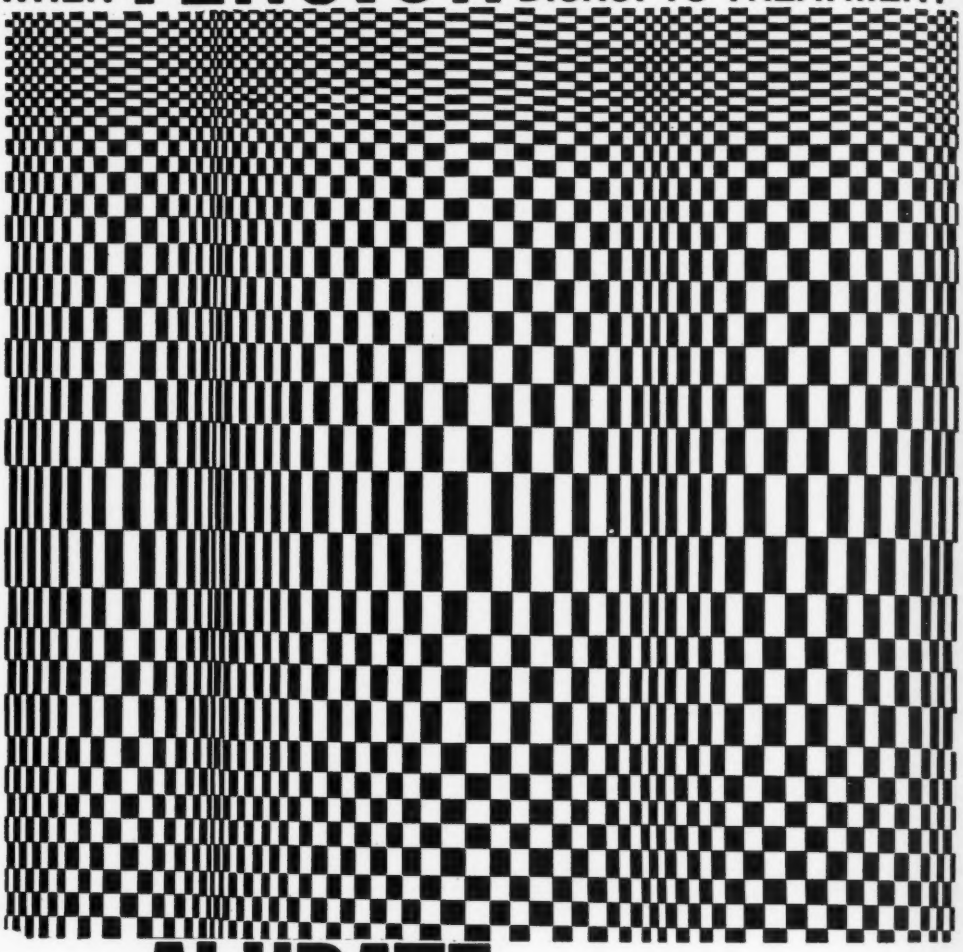
CH-8284

WHEN TENSION DISRUPTS TREATMENT



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Broad margin of safety. Virtually no drowsiness. Over a quarter century of successful clinical use. Alurate is effective by itself and compatible with a wide range of other drugs. To avoid barbiturate identification or abuse, Alurate is available as Elixir Alurate (cherry-red) and Elixir Alurate Verdum (emerald-green).

Adults: ½ to 1 teaspoonful of either Elixir Alurate or Elixir Alurate Verdum, 3 times daily. ALURATE®—brand of aprobarbital.

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Diagnostic Quandaries

Colitis? Gall Bladder Disease?
Chronic Appendicitis?
Rheumatoid Arthritis? Regional Enteritis?

A DISEASE that is frequently overlooked in solving diagnostic quandaries is amebiasis. Its symptoms are varied and contradictory, and diagnosis is extremely difficult. In one study, 56% of the cases would have been overlooked if the routine three stool specimens had been relied on.[1]

Another study found 96% of a group of 150 patients with rheumatoid arthritis were infected by *E. histolytica*. In 15 of these subjects, nine stool specimens were required to establish the diagnosis.[2]

Webster discovered amebic infection in 147 cases with prior diagnoses of spastic colon, psychoneurosis, gall bladder disease, nervous indigestion, chronic appendicitis, and other diseases. Duration of symptoms varied from one week to over 30 years. In some cases, it took as many as six stool specimens to establish the diagnosis of amebiasis.[3]

Now treatment with Glarubin provides a means of differential diagnosis in suspected cases of amebiasis. Glarubin, a crystalline glycoside obtained from the fruit of *Simarouba glauca*, is a safe, effective amebicide. It contains no arsenic, bismuth, or iodine. Its virtual freedom from toxicity makes it practical to treat suspected cases without undertaking difficult, and frequently undependable, stool analyses. Marked improvement following administration of Glarubin indicates pathologically significant amebic infection.

Glarubin is administered orally in tablet form and does not require strict medical supervision or hospitalization. Extensive clinical trials prove it highly effective in intestinal amebiasis.

Glarubin*

TABLETS

specific for intestinal amebiasis

Supplied in bottles of 40 tablets, each tablet containing 50 mg. of glaucarubin.

Write for descriptive literature, bibliography, and dosage schedules.

1. Cook, J.E., Briggs, G.W., and Hindley, F.W.: Chronic Amebiasis and the Need for a Diagnostic Profile, Am. Pract. and Dig. of Treat. *6*:1821 (Dec., 1955).

2. Rinehart, R.E., and Marcus, H.: Incidence of Amebiasis in Healthy Individuals, Clinic Patients and Those with Rheumatoid Arthritis, Northwest Med., *54*:708 (July, 1955).

3. Webster, B.H.: Amebiasis, a Disease of Multiple Manifestations, Am. Pract. and Dig. of Treat. *9*:897 (June, 1958).

*U.S. Pat. No. 2,864,745

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Maximal Absorption
Acid stable, highly soluble

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Maximal Flexibility
May be administered without regard to meals. However, highest absorption is achieved when taken just before or between meals.

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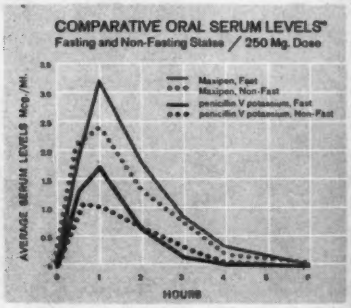
Indicated in infections caused by streptococci, pneumococci, susceptible staphylococci, and gonococci



*Based on 3294 individual serum antibiotic determinations. Complete details available on request.

DOSAGE: For moderately severe conditions, 125 to 250 mg. three times daily. For more severe conditions, 500 mg. as often as every four hours around the clock.

NOTE: To date, MAXIPEN has not shown less allergic reactions than older oral penicillins. Usual precautions regarding penicillin administration should be observed.

SUPPLIED: MAXIPEN TABLETS, scored, 125 mg. (200,000 units), bottles of 36; 250 mg. (400,000 units), bottles of 24 and 100 tablets. MAXIPEN FOR ORAL SOLUTION; reconstituted each 5 cc. contains 125 mg. (200,000 units), in 60 cc. bottles.

MAXIPEN, the orally maximal penicillin, is a triumph of man over molecule; a product of Pfizer Research

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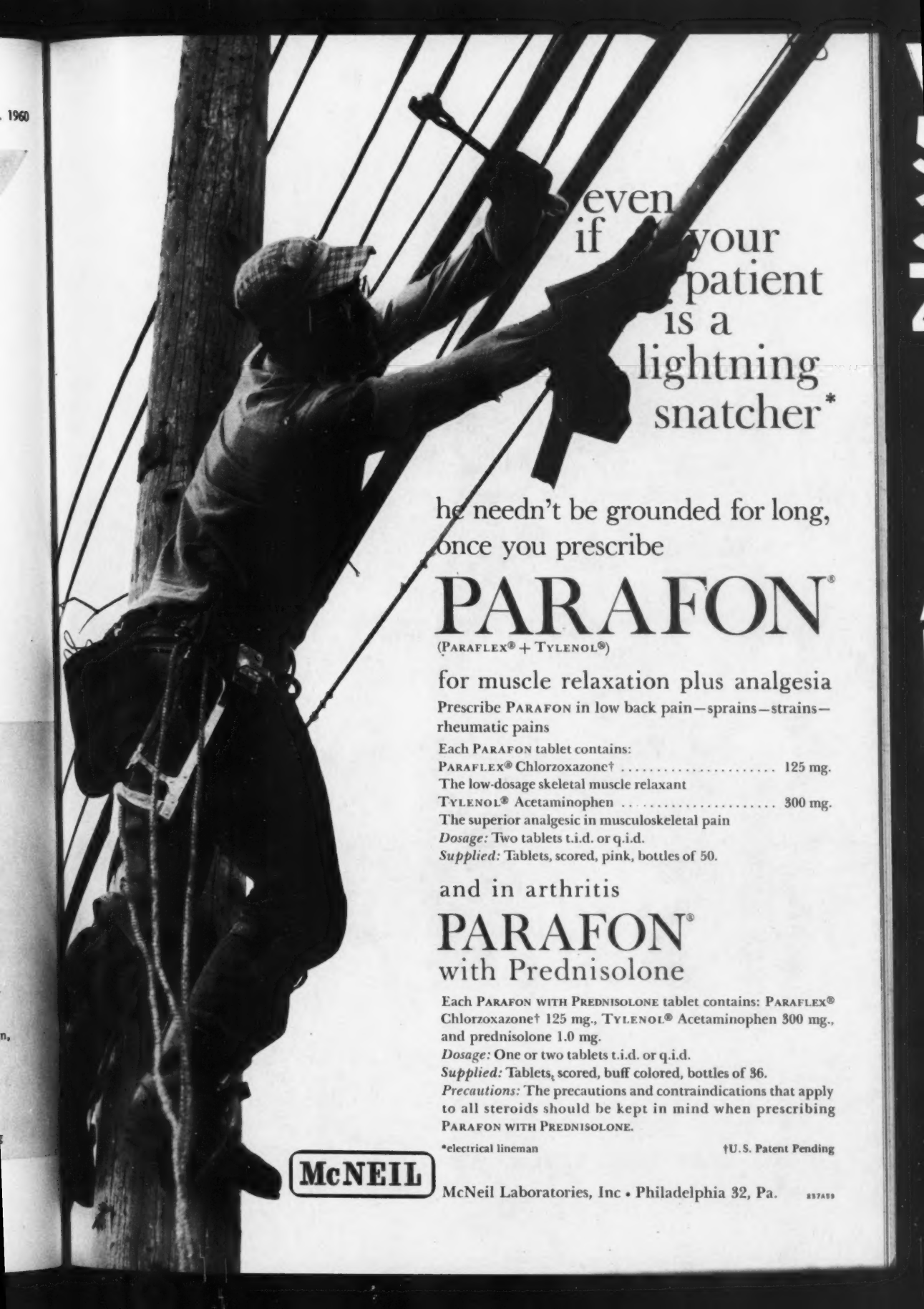
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Each cc. contains:
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Available in dropper bottles of 10 cc.

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Literature available on request.

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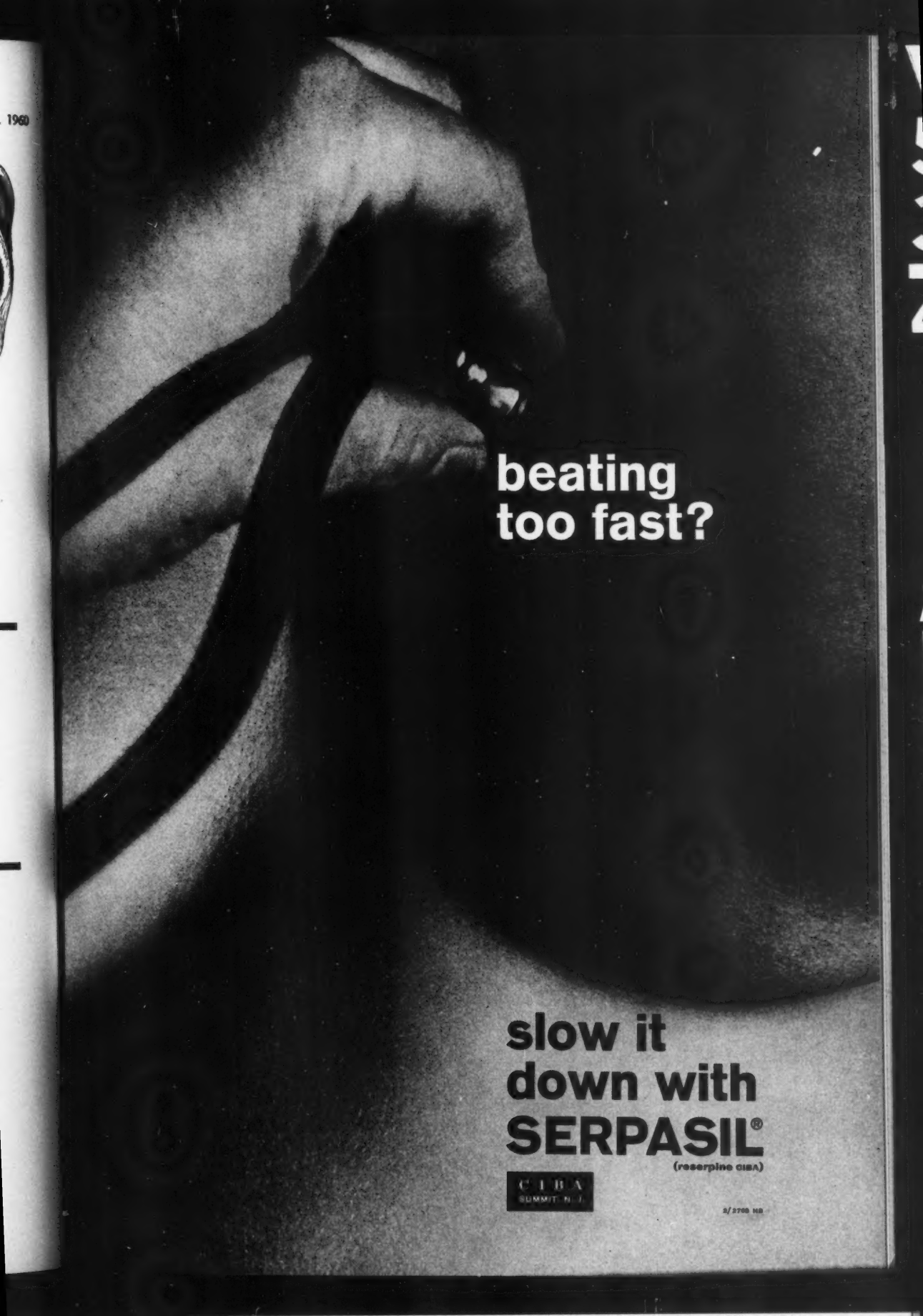
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Rautensin bibliography: 1. WRIGHT, W. T., JR.; POKORY, C., AND FOSTER, T.: AM. PRACT. & DIGEST. TREAT. 7:1992, 1956. 2. SUCKLE, E.: GERIATRICS 11:509, 1956. 3. FINCH, W. J.: J. OKLAHOMA M.A. 50:259, 1957. 4. TERMAN, L. A.: ILLINOIS M. J. 3:67, 1957. 5. GIFFORD, R. W.: J. ARKANSAS M. SOC. 55:31, 1958. 6. FORD, R. V., AND MOYER, J. H.: POSTGRAD. MED. 23:41, 1958.

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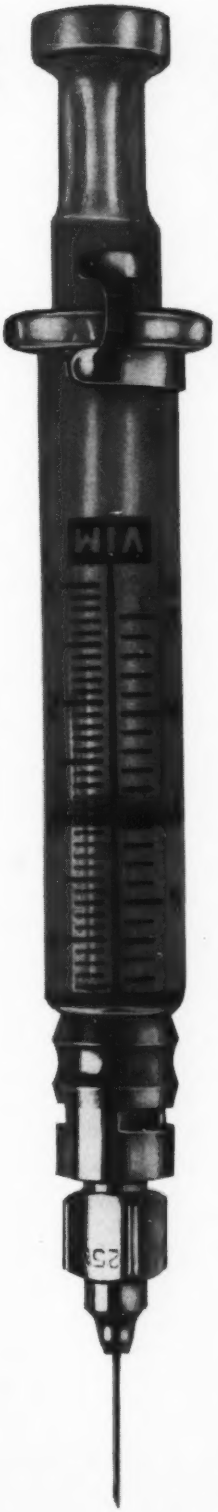

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Pearl River, New York

Continued from page 68

Drs. R. Emmett Kelly and Jerome I. Simon, both of St. Louis, have been appointed as National Chairman and Associate Chairman, respectively, of the Medical Alumni Division of the St. Louis University's 150th anniversary development program.

Dr. John I. Matthews is President of St. Mary's Hospital in Jefferson City. Other officers include Dr. Marshall W. Kelly, Vice-President; and Dr. J. A. Ossmann, Secretary-Treasurer.

New President of the staff of Memorial Hospital at Harrisonville is Dr. Edward S. Jones, Harrisonville. Dr. Basil O. Hartwell, Drexel, is Vice-President; and Dr. H. A. Tracy, Belton, Secretary.

Dr. Theodore Van Ravenswaay, Columbia, has been appointed pathologist at the Ellis Fishel State Cancer Hospital in Columbia.

Dr. Richard G. Pugh has been chosen President-Elect of the medical staff of the Independence Sanitarium and Hospital.

St. Francis Hospital staff at Washington has elected Dr. B. G. Strehlman as President of the medical staff.

Dr. Robert W. Kelley has been elected President-Elect of the Doctors' Foundation in St. Louis.

Officers of the Buchanan County Medical Society include Dr. T. E. Potter, President; Dr. J. M. Hughes, President-Elect; Dr. John R. Forgrave, Vice-President; Dr. William V. Rost, Secretary; and Dr. Robert W. Kieber, Treasurer, all of St. Joseph.

Drs. John Walterscheid and Wyeth Hamlin, both of Hannibal, have been elected President and Secretary-Treasurer, respectively, for the Marion-Ralls-Shelby County Medical Society.

Officers of the Lincoln-St. Charles County Medical Society are Dr. William Poggemeier, President; Dr. V. A. Schneider, Vice-President; and Dr. Paul Rother, Secretary-Treasurer, all of St. Charles.

President of the Boone County Medical Society is Dr. John J. Modlin. Dr. Joseph E. Flynn is Vice-President and Dr. E. L. Washington is Secretary-Treasurer. The doctors are all from Columbia.

Officers of the Greene County Medical Society include Dr. John P. Ferguson, President-Elect; Dr. F. T. H'Doubler, Jr., Secretary; and Dr. William F. Johnson, Treasurer, all of Springfield.

Dr. Henry Sweany, Mount Vernon, is President of the Ozarks Medical Society. Dr. J. D. Bennett, Branson, is Vice-President; Dr. A. J. Graves, Mount Vernon, Secretary-Treasurer; and Dr. F. B. Brown, Aurora, Assistant Secretary.

Officers of the Mid-Missouri County Medical Society include Dr. A. R. Baumann, Steeleville, President; Dr. R. W. Froelich, Lebanon, Dr. E. A. Stricker, St. James, Dr. F. A. Elders, Cuba, Dr. B. J. Vass, Salem, and Dr. C. S. Miller, Waynesville, Vice-Presidents; and Dr. M. K. Underwood, Rolla, Secretary-Treasurer.

New members of county medical societies in Missouri include *Boone:* Drs. Carl H. Almond, David G. Hall, Robert M. Jamison, John H. Landor, and Theodore Van Ravenswaay, all of Columbia; *Buchanan:*

Continued on page 80

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—New England J. Med. *261*:478, 1959 (Schiller, I. W. and Lowell, F. C.)

Dimetane works with an effectiveness of 91% in respiratory allergies —NEW YORK J. MED. 59:3060, 1959 (Fuchs, A. M. and Maurer, M. L.).

In allergic and pruritic dermatoses the effectiveness rate of Dimetane is 94.6% —ANTIBIOTIC MED. & CLIN. THERAPY 6:275, 1959 (Ludowe, I. I.).

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Continued from page 78

Drs. Carleton H. Lee and Charles R. Willman, both of St. Joseph; *Cape Girardeau:* Dr. W. A. Williams, Jr., Cape Girardeau; *Chariton-Macon-Monroe-Randolph:* Dr. E. K. Musson, Macon; and Dr. Charles W. Pemberton, Mendon; *Greene:* Dr. William M. Walker, Springfield; *Marion-Ralls-Shelby:* Dr. Edward M. Plowman, Hannibal; *Mineral Area:* Dr. Charles W. Castain, Jr., Farmington, and Dr. W. Paul Dennis, Flat River; *Ozarks:* Dr. Allen Bailey, Mount Vernon, and Dr. Roy E. Kenney, Neosho; *St. Louis:* Drs. Howard J. Aylward, Joe E. Belew, James W. Clark, Jr., Alan F. Denk, Alvin E. Gaary, Ronald E. Hoffmann, James E. McKittrick, Alexander R. Margulis, James A. Nishi, Melchorl Ongjoco, William I. Stryker, and Kathleen Winters, all of St. Louis; *St. Louis County:* Dr. Elizabeth K. Gay, Florissant, Dr. Wilbur H. Gearhart, St. Louis, Dr. Herbert K. Luke, St. Louis, Dr. Richard M. Margolis, Florissant, Dr. Gunther P. Nagel, St. Louis, and Dr. Brent M. Parker, St. Louis.

New appointments to the University of Missouri Medical Center include Dr. Massoud Eghrari as Assistant Instructor in Surgery and Second Year Resident; Dr. Robert E. Bregant, Assistant Instructor in Medicine; Dr. Morris P. Gordon, Assistant Instructor in Medicine; Dr. Samuel H. Gray, Assistant Instructor in Surgery and First Year Resident; Dr. Loren H. Hartley, Assistant Instructor in Medicine and First Year Resident; Dr. Wilber B. Spalding, Jr., Assistant Instructor in Surgery and First Year Resident; Dr. Gerald Voelkers, Jr., Assistant Instructor in Surgery and First Year Resident; Dr. James E. Bumgarner, Clinical Instructor in Urology; Dr. Herbert L. Warren, Clinical Instructor in Urology; Dr. Howard D. Adams, Assistant Instructor and Second Year Resident in Medicine; and Dr. Robert W. Moellenhoff, Assistant Instructor in Pathology.

Officers of the Kansas City Southwest Pediatrics Society include Dr. T. F. Edwards, President; Dr. Gerald E. Hughes, Vice-President; and Dr. Richard D. Bliss, Secretary-Treasurer.

Dr. Robert D. Ryan, St. Louis, is Treasurer of the American Association for the Study of Headache.

Officers of the St. Louis Dermatological Society are Dr. Calvin C. Ellis, President; Dr. Lawrence K. Halpern, Vice-President; and Dr. James C. Sisk, Secretary.

Dr. Hilliard Cohen has been elected President of the Community Blood Bank of Kansas City. Drs. Adolph R. Pearson and Walter V. Corburn were elected Vice-Presidents, and Dr. Carrol P. Hungate was chosen Secretary-Treasurer.

Medical staff officers at St. Joseph's Hospital include Dr. W. Wilmot Gist, President; Dr. Paul R. Wright, President-Elect; Dr. Daniel J. Cutcliff, Secretary; and Dr. Donald K. Piper, Treasurer, all of St. Joseph.

Dr. J. Earl Smith, St. Louis, has been elected to the Board of Directors at the Greater St. Louis Hospital Council.

Dr. Milford T. Kubin has become Administrator of

Continued on page 84

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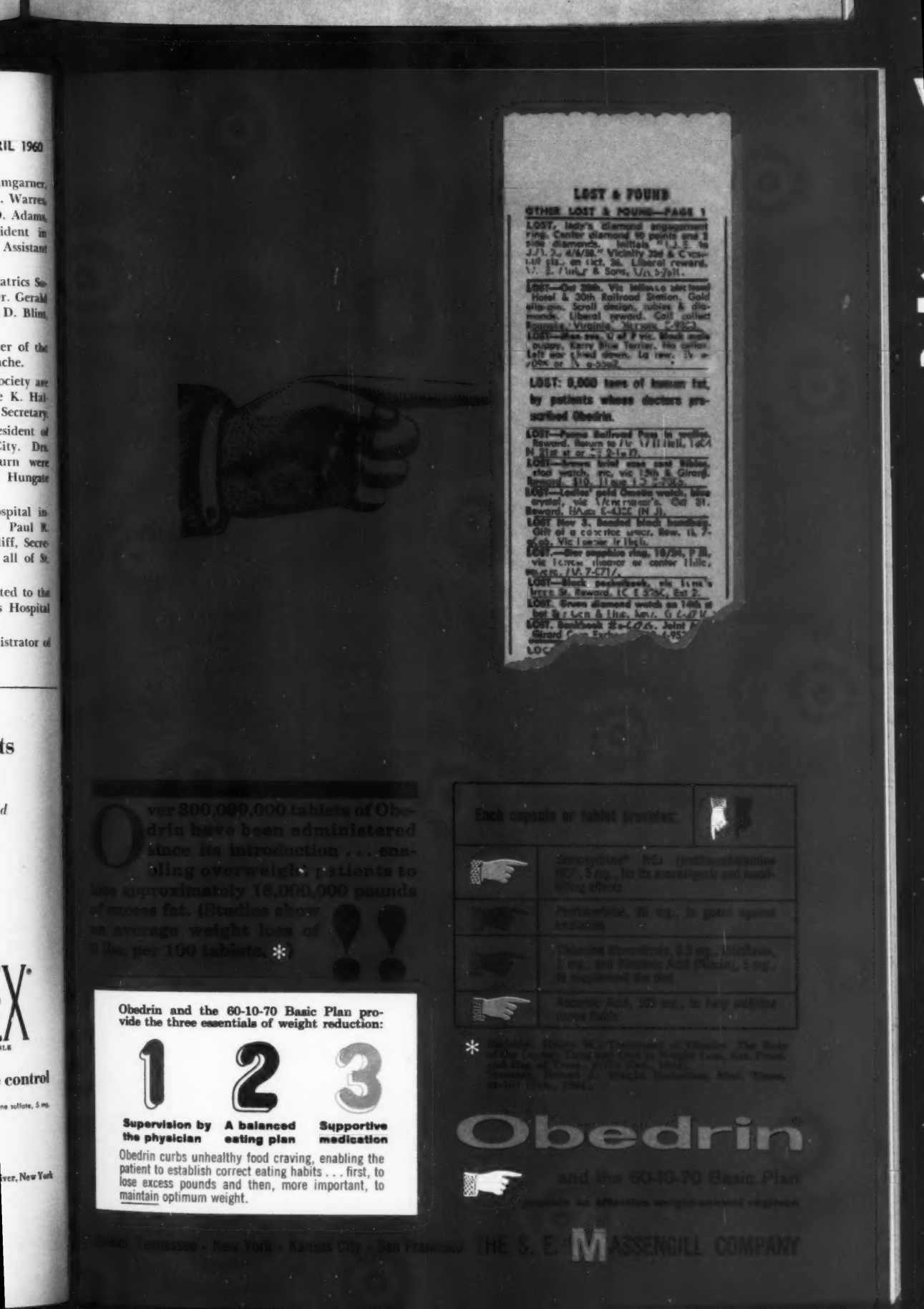
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Obedrin curbs unhealthy food craving, enabling the patient to establish correct eating habits . . . first, to lose excess pounds and then, more important, to maintain optimum weight.
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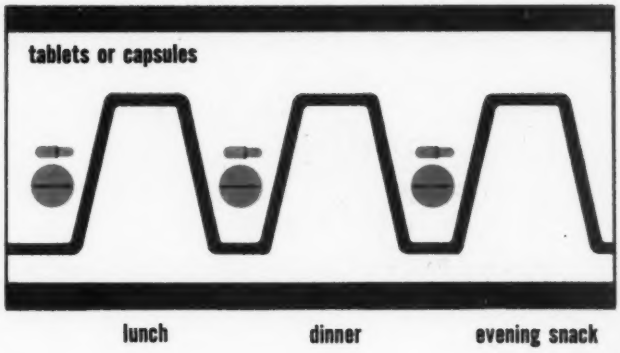
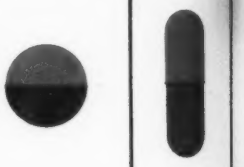


The Obedrin formula permits a flexible dosage schedule to depress the appetite at peak hunger periods. The physician can adjust dosage to fit each patient's need.



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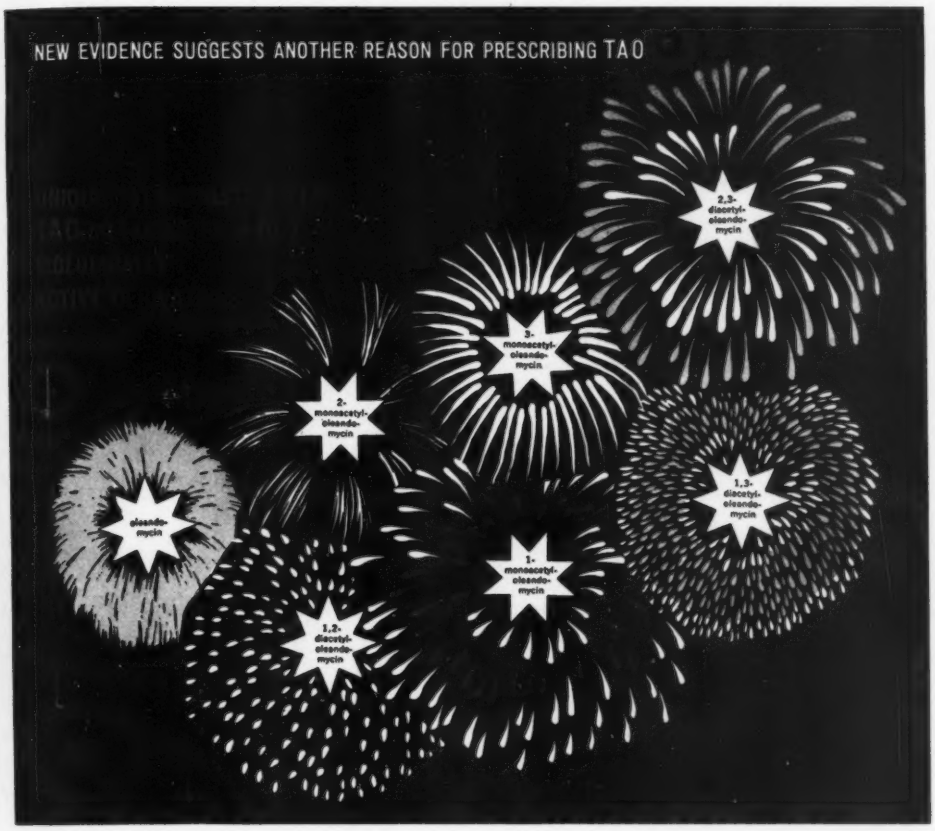

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1. English, A. R., and McBride, T. J.: Proc. Soc. Exper. Biol. & Med. 100:880 (Apr.) 1959. 2. Celmer, W. D.: Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959, p. 277. 3. English, A. R., and Fink, F. C.: Antibiotics & Chemother. 8:420 (Aug.) 1958.

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Continued from pgae 80

the Ellis Fischel State Cancer Hospital in Columbia.

New officers of the Missouri Methodist Hospital, St. Joseph, are Dr. Manning E. Grimes, President; Dr. Thompson E. Potter, President-Elect; Dr. John R. McDaniel, Vice-President; and Dr. Warren C. Baker, Savannah, Secretary-Treasurer.

Staff officers at St. Elizabeth's Hospital, Hannibal, recently elected are Dr. R. J. Lanning, President; Dr. J. H. Walterscheid, Vice-President; and Dr. John Canella, Secretary.

Dr. Robert E. Dunshee is President of St. Francis Hospital staff, in Maryville. Dr. G. R. Wempe is Vice-Chief and Dr. H. C. Bauman is Secretary.

Officers of the Samaritan Hospital, Macon, are Dr. Donald E. Eggleston, President; and Dr. Howard Miller, Vice-President.

NORTH CAROLINA

Dr. Henry G. Gramblett, has joined the faculty of Bowman Gray School of Medicine as Associate Professor of Pediatrics, Director of the Virology Laboratory and Associate in Microbiology and Pathology.

Dr. James A. Harrill, Professor of Otolaryngology at the Bowman Gray School of Medicine, has been chosen President-Elect of the Forsyth County Medical Society.

New members of the Medical Society of the State of North Carolina are Drs. John W. Barnard and Robert C. Smith, Banner Elk; Dr. Jack B. Perkins, Southport; Dr. Claude B. Goswick, Hendersonville; and Drs. Arthur S. Morris and John F. Ditunno, Jr., Hot Springs.

Dr. A. J. Bambara has been appointed a U. S. Public Health Service practitioner trainee in the Department of Psychiatry of the University of North Carolina School of Medicine.

Dr. Harold D. Green, Professor of Physiology and Pharmacology at the Bowman Gray School of Medicine of Wake Forest College, has been appointed to the editorial board of *Circulation Research* for a period of 5 years.

OKLAHOMA

Dr. Peter E. Russo, Oklahoma City, has been chosen President-Elect of the Rocky Mountain Radiological Society.

New appointments to the University of Oklahoma School of Medicine faculty are Drs. Stephen Wright Thompson and Natoo C. Patel, Department of Medicine; Dr. Leon Horowitz, Department of Pediatrics; Dr. Joseph L. Martin, Department of Anesthesiology; and Dr. Everett N. Holden, Department of Preventive Medicine and Public Health.

Dr. R. L. Currie, Stilwell, and Dr. R. H. Mayes, Duncan, have been appointed County Superintendents of Health of their respective counties, Adair and Jefferson.

Dr. Robert C. Lawson, Oklahoma City, has been appointed to the Board of State Governors of the American Diabetes Association.

Continued on page 86

Appalachian Hall • Asheville, North Carolina

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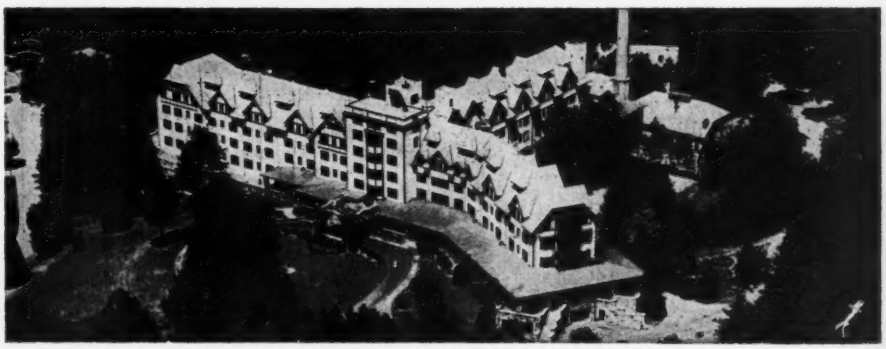

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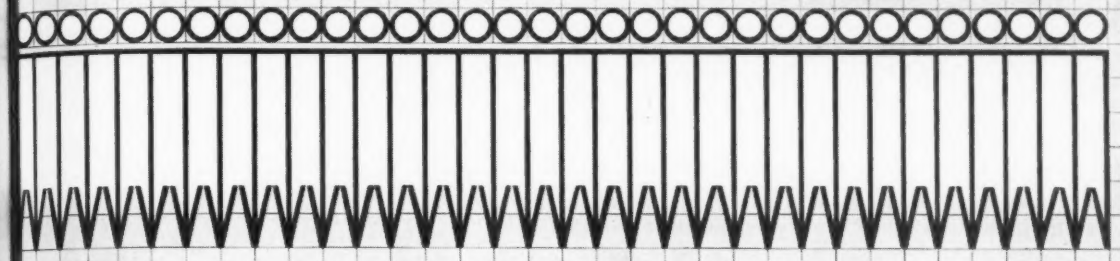
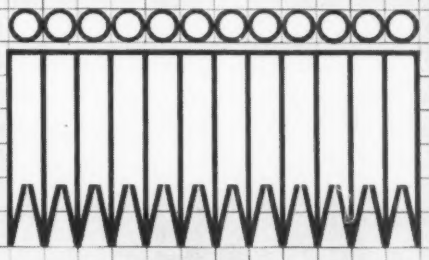
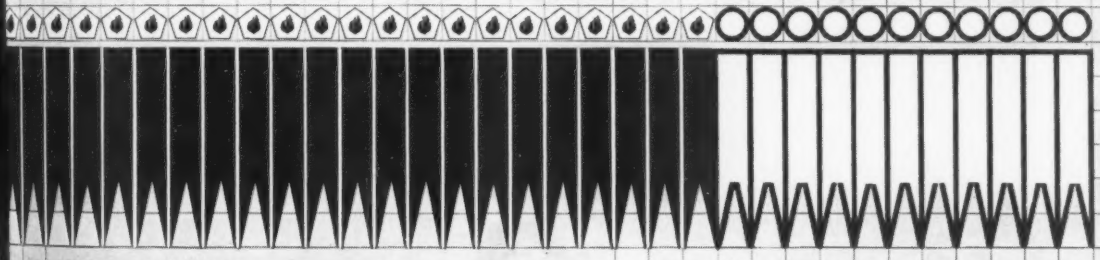


Of 45 arthritic patients
who were refractory
to other corticosteroids*





22 were successfully
treated with **Decadron**[1,2]

1. Boland, E. W., and Headley, N. E.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.
2. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.

*Cortisone, prednisone and prednisolone.

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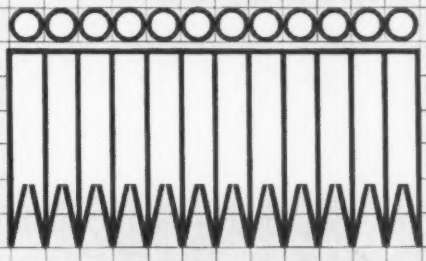

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Continued from page 84

Dr. J. B. Hollis, Mangum, has been appointed Chairman of the National Rehabilitation Committee of the American Legion.

The Tulsa County Medical Society has 15 new members: Drs. Joe Burge, Duane E. Brothers, Nathan A. Cohen, Kenneth C. Duncan, Jack E. Hale, William L. Harris, John E. Kauth, Kenneth L. Knuth, C. Frank Knox, Jr., Richard A. Liebendorfer, Dwane B. Minor, Jack W. Newport, Hobart C. Sanders, and Francis W. Pruitt, all of Tulsa, and Dr. David C. Clemans, Skiatook.

Dr. Lynn Barnes, Nowata, has been named local President of the Chamber of Commerce for 1960.

Dr. Carles W. Letcher, Miami, retired from the Navy, has received a commission as Rear Admiral (Medical Corps), United States Naval Reserve.

Dr. William W. Schottstaedt, University of Oklahom Medical Center faculty member, has been named Chairman of the Department of Preventive Medicine and Public Health.

SOUTH CAROLINA

New officers of the Medical Society of South Carolina are Dr. A. J. Buist, Jr., President; Dr. Ralph R. Coleman, Vice-President; Dr. F. M. Ball, Secretary-Treasurer; and Dr. J. I. Waring, Librarian, all of Charleston.

Dr. James R. Young, Anderson, Director of Rose E. Ramer Cancer Clinic of Anderson Memorial Hospital, has been elected a Director of the American Cancer Society.

Officers of the York County Medical Association include Dr. James L. Simpson, President; Dr. W. H. Williams, Jr., Vice-President; and Dr. W. R. Ward, Jr., Secretary, all of Rock Hill.

Two staff members of the research laboratory of the U. S. Public Health Service in Columbia have received honors. Dr. Geoffrey M. Jeffery has received the Bailey K. Ashford Award for outstanding work in the field of tropical medicine. Dr. Martin D. Young, Director of the laboratory, has been named Editor of *The American Journal of Tropical Medicine and Hygiene* for this year.

President of the Charleston County Medical Society is Dr. J. I. Waring; Vice-President is Dr. Harold Pettit; and Secretary-Treasurer, Dr. R. Maxwell Anderson.

Dr. A. W. Lowman, Denmark, has been elected President of the Seaboard Air Line Surgeons.

Dr. Robert F. Hagerty, Charleston, is Vice-President of the Southeastern Society of Plastic and Reconstructive Surgeons.

The Columbia Veterans Administration Hospital has appointed Dr. Philip P. Claytor a staff physician and Dr. Edward S. Cardwell has been reappointed Chief of Laboratory Service. Dr. Karl M. Lippert, Chief of Surgery of the Hospital, has been named

Continued on page 87

"Brewers' yeast is an excellent source of protein of high biologic value and of the vitamins of the B complex.... When it is desired to give additional vitamins of the B complex and to add to the protein quota of the diet, this food can profitably be incorporated in other foods."*

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*Mitchell, J. S., and Darby, W. J., Nutrition and Diet in Health and Disease, ed. 6, Philadelphia, Saunders, 1948, p. 113.

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WANTED—Internist for 40-bed acute medical ward. Board certified or Board eligible preferred. Salary dependent upon qualifications. Limited number of station housekeeping quarters. Golfing and hunting in immediate vicinity. Resort areas within motoring distance. Contact Manager, VA Center, Dublin, Georgia.

WANTED—Psychiatrist for 35-bed intensive treatment ward. Board certified or Board eligible preferred. U. S. citizenship and licensure required. Salary dependent upon qualifications. Golfing and hunting in immediate vicinity. Resort areas within motoring distance. Limited number of station housekeeping quarters. Contact Manager, VA Center, Dublin, Georgia.

WANTED—Internist and Pediatrician. A well established obstetrician-gynecologist, ophthalmologist, otolaryngologist and general surgeon, wish to add an internist and pediatrician to their group; mid-west location near large city; complete laboratory facilities under the auspices of a registered medical technologist; x-ray facilities under the direction of a radiologist. Contact SVA, c/o SMJ.

WANTED—General surgeon for staff physician on 115-bed service. Board certified or Board eligible. U. S. citizenship and licensure required. Salary dependent upon qualifications. Limited number of station housekeeping quarters. Golfing and hunting in immediate vicinity. Resort areas within motoring distance. Contact Manager, VA Center, Dublin, Georgia.

Continued from page 86

Area Chief of Surgery for Veterans Administration Area 7.

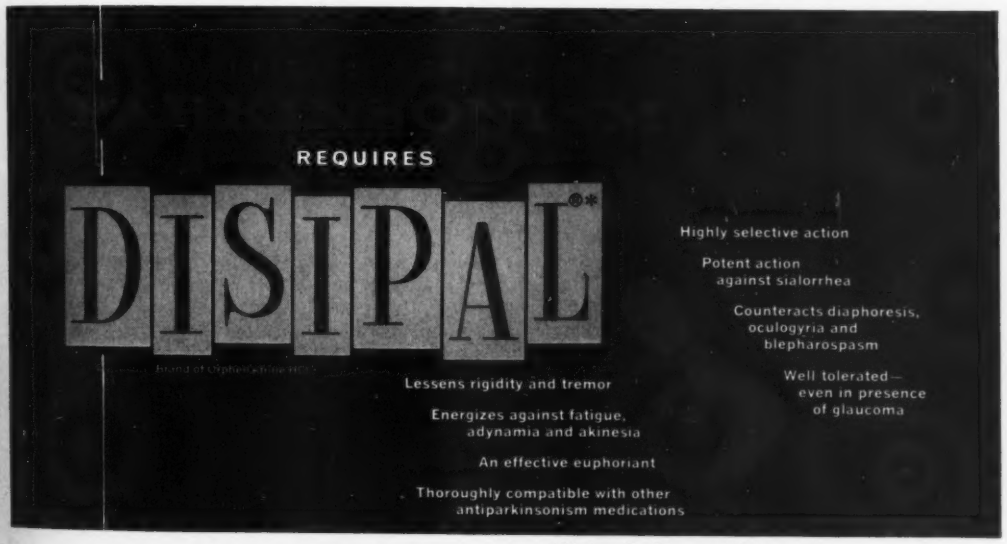
Officers of the Pee Dee Medical Society include Dr. Elliott Finger, Marion, President; Dr. Randy Elvington, Nichols, President-Elect; Dr. Ed Rice, Mullins, Vice-President; and Dr. D. G. Kitchens, Marion, Secretary-Treasurer.

Dr. A. S. Pearson, Woodruff, has been named Spartanburg County "Doctor of the Year."

Dr. J. I. Converse is the new President of the Greenville County Medical Society. Other officers include Dr. Horace Whitworth, President-Elect; Dr. L. H. Taylor, Vice-President; Dr. John C. Muller, Secretary; and Dr. Willis S. Hood, Treasurer. The physicians are all of Greenville.

Dr. Harwood Beebe has been re-elected Chief of Staff at Mary Black Hospital in Spartanburg. Others

Continued on page 90



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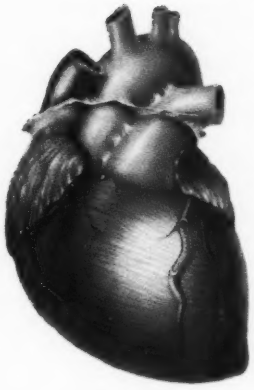

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REFERENCES

1. Ellis, L. B. *et al.*: Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J. E. F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.*: Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

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Continued from page 87

elected are Dr. Allen B. Warren, Vice-Chief of Staff; Dr. Sam Orr Black, Jr., Secretary; and Drs. Charles B. Hanna and Clarence C. Lyles, Executive Committee members.

Officers of the Anderson County Medical Society include Dr. Joel Wyman, President; Dr. Charles Browne, Vice-President; Dr. Thomas A. Collins, Secretary; and Dr. J. W. Jackson, Treasurer; all are from Anderson.

TENNESSEE

Officers of the Memphis Obstetrical and Gynecological Society include Dr. Glen H. Williams, President; Dr. William T. Black, Vice-President; Dr. Charles R. Riggs, Secretary; and Dr. John Palmer Moss, Treasurer.

Dr. Robert A. Greer Ricketson, Nashville, is President of the Southeastern Society of Plastic and Reconstructive Surgeons.

Dr. Dorothy L. Brown, Nashville, is a Fellow in the American College of Surgeons.

Elected to the medical staff of the Maury County Hospital in Columbia were Dr. Carl C. Gardner, Jr., President; Dr. Harry C. Helm, Vice-President; and Dr. Ambrose M. Langa, Secretary-Treasurer.

Dr. John T. Carter, Jr., has been elected President of the Germantown Civic Club.

Dr. J. Hughes Chandler has been elected Chief of the medical staff at Jackson-Madison County General Hospital. Dr. Harold T. McIver is Assistant Chief. Other chiefs of services include: Drs. Thomas K. Ballard, Fred M. Friedman, Chester L. Holmes, S. Allen Truex, John R. Thompson, Chester K. Jones, and Henry N. Moore. The physicians are all of Jackson.

Officers of the Warren County Medical Society include Dr. John T. Mason, President; Dr. J. E. Phillips, Vice-President; and Dr. Elizabeth M. Lodge, Secretary-Treasurer, all of McMinnville.

Dr. Charles D. Huffman, Limestone, is the new Director of the Greene County Health Department.

Recently installed as officers of the Chattanooga-Hamilton County Medical Society were Dr. George K. Henshall, President; Dr. Augustus McCravey, President-Elect; and Dr. Charles Hawkins, Secretary-Treasurer, all of Chattanooga.

Dr. Richard A. Miller has been elected Chief of the medical staff of the Memphis Eye, Ear, Nose and Throat Hospital. Other officers are Dr. T. P. Manigan, Vice-Chief, and Dr. Eugene Vacarro, Secretary, all of Memphis.

Dr. N. E. Hyder, Erwin, has been elected President of the John Sevier Chapter of the Tennessee Academy of General Practice.

Officers of the Holston Valley Community Hospital include Dr. H. J. Brown, President; Dr. Frank B. O'Connell, President-Elect; and Dr. Lyle Smith, Secretary-Treasurer, all of Kingsport.

Dr. William G. Stephenson, Chattanooga, has been

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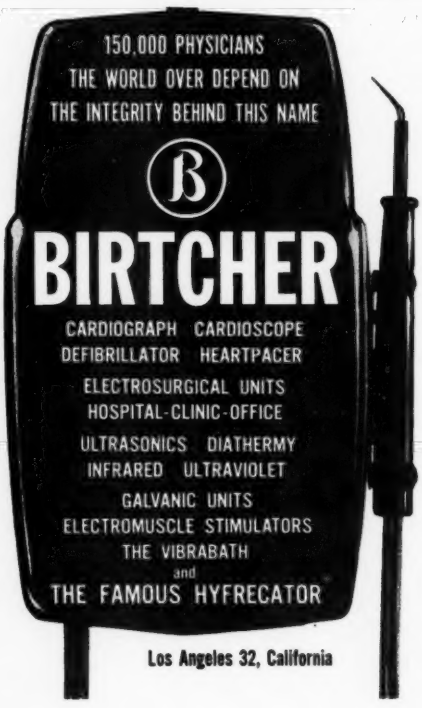

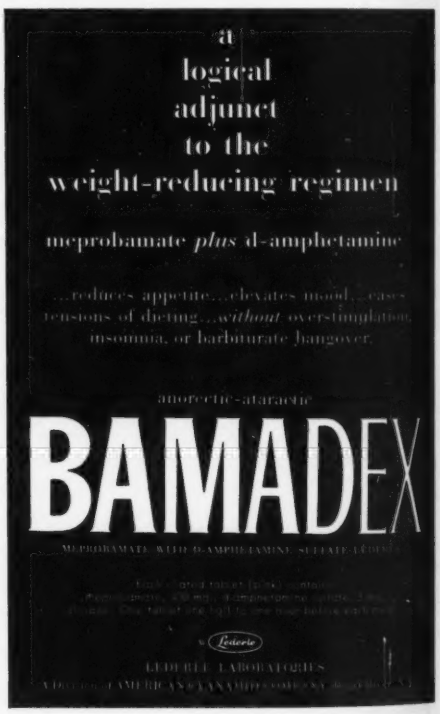

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REFERENCES: 1. Barrett, M. E.: J. M. Assoc. Alabama 26:144, 1956. 2. Youngblood, V. H.: J. Urol., Balt., 70:926, 1953. 3. Youngblood, V. H.; Tomlin, E. M.; Williams, J. O. and Kimmelstiel, P.: Tr. Southeast. Sect. Am. Urol. Assoc., Atlanta, Ga. (Apr. 7-11) 1957, p. 40-43. 4. Youngblood, V. H.; Tomlin, E. M. and Davis, J. B.: J. Urol., Balt., 78:150, 1957.

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Continued from page 90

named to the advisory board of the Monticello Insurance Company.

Dr. I. H. Jones is President of the Henry County Medical Society. Other officers include Dr. John Neumann, Vice-President; and Dr. W. G. Rhea, Secretary-Treasurer. The physicians are all of Paris.

TEXAS

Dr. Titus H. Harris, Galveston, has been honored by the founding of the Titus Harris Psychiatric Club. Twenty of his former residents at the University of Texas Medical Branch formed the club and elected the following officers: Dr. Abe Hauser, Houston, President; Dr. Martin L. Towler, Galveston, Vice-President; Dr. E. I. Bruce, Galveston, Secretary-Treasurer; and Dr. Edgar Ezell, Fort Worth, Counselor.

Dr. Charles W. Daeschner, Jr., Houston, Associate Professor of Pediatrics at Baylor University College of Medicine, has been appointed Professor of Pediatrics and Chairman of the Pediatrics Department of the University of Texas Medical Branch.

Governor Price Daniel has appointed Dr. Van Goodall, Clifton; Dr. Richard L. Stratton, Cuero; and Dr. Edwin E. Connor, Houston, to the new Hospital Licensing Advisory Council. Other appointments by Governor Daniel include those of Dr. Hampton C. Robinson, Houston, and Dr. Vance Terrell, Stephenville, to the State Board of Health.

Dr. Enid Gilbert and Dr. Dan M. Queen, both of Austin, were elected to fellowship in the American Academy of Clinical Pathology.

Dr. Mary Witt Hughes, Texarkana, has been awarded fellowship in the American College of Surgeons.

Dr. Mary Agnes Lancaster, Dallas, has been appointed to the Texas Board of Examiners for Ophthalmic Technicians.

VIRGINIA

Officers of the Fredericksburg Medical Society include Dr. Lloyd F. Moss, President; Dr. William D. Liddle, Vice-President; and Dr. J. E. Grimes, Secretary, all of Fredericksburg.

Dr. John Q. Hatten is President of the Newport News Medical Society. Dr. John W. Massey is Vice-President and Dr. A. C. Stanton, Secretary-Treasurer. The physicians are all of Newport News.

Dr. R. Bryan Grinnan, Jr., Norfolk, has been chosen President-Elect of the Virginia Society of Internal Medicine.

Officers of the Northampton County Medical Society include Dr. William F. Bernart, Nassawadox, President; Dr. Thomas B. Hardman, Cape Charles, Vice-President; Dr. William S. Burton, Nassawadox, Secretary; and Dr. E. M. Kellam, Nassawadox, was named to the Board of Censors.

Dr. Robert V. Terrell is President of the Richmond Academy of Medicine. Dr. E. L. Kendig is President-Elect; and Drs. R. Campbell Manson and Carrington Williams, Jr., Vice-Presidents. All are of Richmond.

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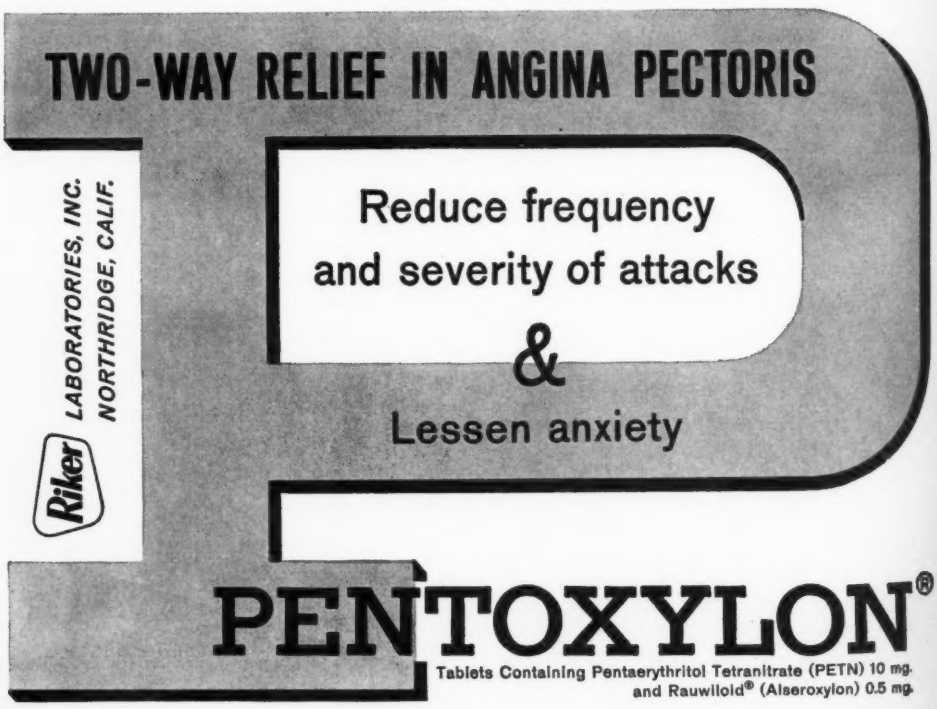
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Continued from page 92

The Medical Society of Northern Virginia has elected Dr. Bradford Bennett, Winchester, President; Dr. Dennis P. McCarty, Front Royal, Vice-President; and Dr. Robert York, Berryville, Secretary-Treasurer.

Dr. Robert L. Norment has been installed as President of the Arlington Medical Society. Other officers include Dr. Michael A. Puzak, President-Elect; Dr. Sigmund Newman, Vice-President; Dr. Howard O. Mott, Secretary; and Dr. Robert B. Neu, Treasurer, all of Arlington.

Dr. George Speck is President of the Alexandria Hospital staff and Dr. John E. Roberts is President-Elect.

Dr. George G. Ritchie, Jr., Richmond, has been re-elected President of the Christian Youth Corps of America.

Dr. E. Palmore Irving, Petersburg, has been chosen President of the Will Rogers Tent, Circus Saints and Sinners.

Officers of the Virginia Baptist Hospital medical staff in Lynchburg include Dr. L. M. Howard, Jr., President; Dr. H. L. Riley, Jr., Vice-President; and Dr. Parker H. Lee, Secretary.

Dr. Gordon E. Shull, Big Stone Gap, has been chosen President of the St. Mary's Hospital in Norton. Dr. Joseph Phillips, Norton, is Vice-President; and Dr. John H. Dellinger, Norton, Secretary.

The Richmond Memorial hospital staff has elected Dr. Benjamin W. Rawles, Jr., Chief of Staff; Dr. Meyer Vitsky, Vice-Chief of Staff; and Dr. Fleming Gill, Secretary.

Dr. T. B. Payne has been elected President of the staff of the Mary Washington Hospital, Fredericksburg. Dr. James G. Willis is Vice-President; and Dr. T. Stacy Lloyd, Secretary.

Dr. C. C. Powel, Harrisonburg, has been re-elected President of the Rockingham Cerebral Palsy Treatment Center.

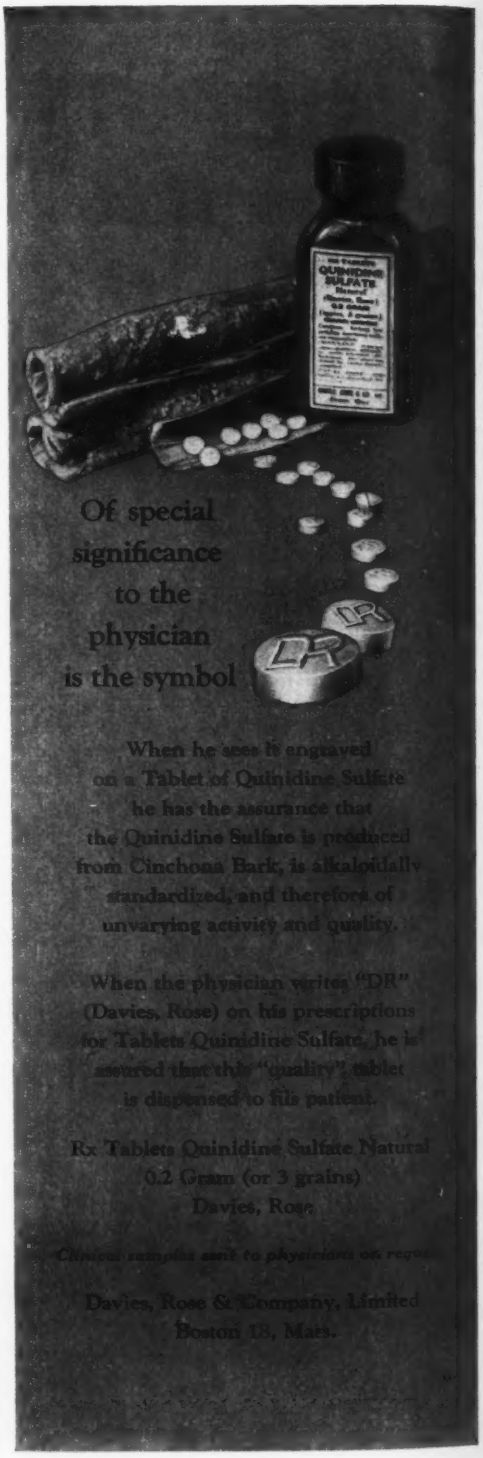
New members of the Medical Society of Virginia include Dr. Stuart B. White, Blackstone; Dr. Robert J. Buchanan, Churchland; Dr. John M. Stoneburner, Danville; Dr. Jan Marimus, Fries; Dr. Frederick W. Shillinger, Hampton; Dr. Jerome D. Perlman, Norfolk; Dr. Eugenia Urbanovich, Petersburg; Drs. Richard H. Egdahl and Lester L. Gillespie, Richmond; Drs. Edward C. Bauer and William H. Sipe, Roanoke; and Drs. Doris L. A. Thurman, and William A. Thurman, Jr., Vinton.

WEST VIRGINIA

Dr. Randolph L. Anderson, Charleston, has been named a member of The American Orthopaedic Association.

Officers of the Eastern Panhandle Medical Society are Dr. George F. Pugh, Jr., President; Dr. Jules F. Langlet, First Vice-President; Dr. N. B. Groves, Second Vice-President; and Dr. R. A. Hamilton, Jr., Secretary-Treasurer, all of Martinsburg.

The Mercer County Medical Society has elected the following officers: Dr. W. E. Copenhaver, President; Dr. Henry F. Warden, Jr., Vice-President; and Dr. John J. Mahood, Secretary-Treasurer, all of Bluefield.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The Birtcher Corporation	90
Brawner's Sanitarium	88
Brayten Pharmaceutical Corporation	65
Burroughs Wellcome & Company, Inc.	74
Ciba Pharmaceutical Products, Inc.	62, 75
Davies, Rose & Company, Ltd.	94
Desitin Chemical Company	18
Dewberry Engraving Company	86
Drug Specialties, Inc.	78
Eaton Laboratories	17, 34, 56, 81, 91
Endo Laboratories, Inc.	7
Geigy Pharmaceuticals	39
Hill Crest Sanitarium	64
Hynson, Westcott & Dunning, Inc.	48
Irwin, Neisler & Company	opp. 16, 43
Lederle Laboratories Division, American Cyanamid Company	4-5, 23, 33, 50, 64, 67, 68, 77, 80, 90
Eli Lilly and Company	3rd Cover
The S. E. Massengill Company	opp. 32, 71, opp. 80
McNeil Laboratories, Inc.	19, 52, 73
Merck Sharp & Dohme	20-21, 58, 85
Mobac Laboratories	36
Parke, Davis & Company	4th Cover
Pfizer Laboratories	14, 45
Pharmacia Laboratories, Inc.	2
Picker X-Ray Corporation	51
Pitman-Moore Company	41
Wm. P. Poythress & Company, Inc.	53
Riker Laboratories, Inc.	1, 63, 87, 92
A. H. Robins Company, Inc.	3, 31, 42, 54-55, 79
Roche Laboratories, Division of Hoffmann-La Roche, Inc.	11, 24-25, 70
J. B. Roerig & Company	8-9, 30, 72, 83
Saint Albans Hospital	68
Sanborn Company	22
Schering Corporation	35, 60
G. D. Searle & Company	49, 61
Smith-Dorsey Division, The Wander Company	16, 40, 59, 76, 93
Smith Kline & French Laboratories	15, 46, 57
E. R. Squibb & Sons	44
Tailby-Nason Company, Inc.	26
First Texas Pharmaceuticals, Inc.	88
Tucker Hospital, Inc.	88
Fifth United States Civil Service Region	80
United States Bond	82
U. S. Vitamin & Pharmaceutical Corporation	28-29
VanPelt & Brown, Inc.	10
Vitamin Food Company, Inc.	86
Wallace Laboratories	12-13, 37, 47, 69, 89, 95
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Winthrop Laboratories	27, opp. 64

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